

# Glossary

**Autonomic regulation** Regulation by the autonomic nervous system. This system regulates a number of cardiovascular and other quantities. Cardiovascular quantities regulated include heart rate, cardiac contractility, resistance, compliance, and unstressed volume. Cardiovascular autonomic regulation is mediated by the baroreflex system, via the sympathetic and parasympathetic systems.

**Baroreflex regulation** Regulation mediated via stimulation of the baroreceptors which are stretch sensors located in the blood vessels of most mammals. In humans high-pressure receptors can be found in the aortic arch and the carotid sinuses, and low-pressure receptors can be found in large systemic veins, in pulmonary arteries, and in the walls of the right atrium. In response to stretch due to pressure change, baroreceptors induce changes in sympathetic and parasympathetic outflow, which in turn give rise to changes in heart rate, cardiac contractility, vascular tone (primarily through high-pressure receptors) and unstressed volume and blood volume (primarily through low-pressure) receptors.

**Blood gases** Gases transported in the blood; typically used to refer to the blood gases oxygen and carbon dioxide involved in respiration.

**Cerebral autoregulation** Autoregulation occurring in the brain. The brain autoregulates to maintain blood flow despite changes in blood pressure. It is believed that autoregulation is primarily mediated via myogenic and metabolic regulation.

**Cheyne-Stokes breathing** A respiratory abnormality characterized by alternate periods of hyperventilation and apnea.

**Closed loop model** A model where the outputs of the model are incorporated in a feedback loop to influence system response or function (compare open loop).

**Euvolemia** Normal amount of intravascular volume for a given body size.

**Exercise hyperpnea** Increase in respiratory ventilation in proportion to metabolic demand without essential deviation of blood  $\text{CO}_2$  tension during muscular exercise.

It is in contrast to chemoreflex in which ventilation increases in proportion to change in blood CO<sub>2</sub> tension.

**Head-up tilt** A laboratory test to examine the cardiovascular response to orthostasis. The test passively tilts a subject from supine to approximately 70° angle.

**Homeostasis** The property of a system to regulate its internal environment in order to maintain a stable and constant condition.

**Hypovolemia** Reduced amount of intravascular volume for a given body size.

**Ill-conditioned estimation** Parameter estimation problem in which the numerical values of the parameter estimates depend strongly on small changes in input data.

**Inverse problem** A general framework for using observed measurements to infer information about the system under investigation.

**Kalman filter** A set of mathematical equations for estimating the state of a process, taking explicitly into account measurement errors and taking measurement data into account incrementally (on-line estimation).

**Metabolic regulation** Regulation of local blood flow mediated via enzymes regulating metabolic pathways in response to changes in the cell's environment, level of metabolism, or signals from other cells. In the cerebral vasculature, for example, an increase in tissue metabolism in an activated nerve area will induce an increase in local blood flow, providing an increase in oxygen and nutrients to the tissues. A subsequent reduction in activity results in blood vessels constriction with local blood flow returning to normal.

**Model validation** The process of testing the correctness of a model. This involves many steps including testing for reasonable model behavior in a variety of conditions with all state variables producing consistent and physiologically reasonable outputs for reasonable parameter values. In essence, one searches for the conditions under which the model behaves appropriately. This domain of validity will depend on (simplifying) model assumptions which in turn depend on the goal for which the model is developed. Often, a narrower meaning is given to validation which involves using portions of available data for parameter estimation and then using the estimated parameters with the remaining data to verify that the model can predict additional observed responses. One method used for model validation includes K-fold cross-validation.

**Multiscale modeling** Model design containing multiple scales. These can be multiple scales in time or in space. Examples include models coupling 3D spatial and 1D spatial components, models with both higher dimensions and zero-D models, or models including several scales in time, e.g., a model having some components that resolve dynamics over seconds and other components that resolve over hours.

**Myogenic regulation** The myogenic response (also called the Bayliss effect) regulates contraction of smooth muscles in response to stretch. In the cerebral vasculature, this effect is mainly seen in the arterioles, where an increase in blood pressure causes distension of the arterioles, in response the smooth muscles are constricted. This effect is mediated via calcium signaling and acts to smooth changes induced by perturbations in blood pressure.

**Open loop model** A model formulation in which the outputs of the model are not used to influence system response. Only arbitrary independently chosen model inputs can be applied to the model to influence the system response.

**Orthostatic intolerance** Inability to maintain an upright posture without developing cardiorespiratory signs of impending loss of consciousness (such as dizziness) and potentially leading to actual syncope.

**Parameter estimation** The process of obtaining values for a set of parameters given a model and available data. Typically, the process is carried out using optimization techniques that usually minimize the least squares cost (the sum of squared errors between the observed and computed quantities). Several problems can arise for parameters that are insensitive (i.e., a change in a given parameter does not affect the observed output). In addition parameters may be functionally dependent which can make their unique estimation impossible.

**Parameter identifiability** This term indicates that the parameters of a model can be identified from the knowledge of model behavior for certain scenarios assuming perfect data reflecting such scenarios.

**Parasympathetic regulation** A part of the autonomic nervous system. It is activated via the baroreceptors and function via regulation of acetylcholine. In the cardiovascular system parasympathetic regulation mainly impacts heart rate. Parasympathetic regulation of heart rate is mediated via the Vagus nerve. Parasympathetic regulation is almost immediate and the effect on heart rate can be observed within one cardiac cycle from the sensed change in blood pressure.

**Periodic breathing** Waxing and waning of breathing in a visually cyclic (but not truly periodic) manner.

**Physiological respiratory dead space** Total wasted ventilation in non-perfused, under-perfused, or poorly-mixed alveolar units.

**Respiration** The term respiration is used in several ways. It can refer at the cellular level to the process of generating energy including aerobic respiration (using oxygen and generating carbon dioxide) and anaerobic (not using oxygen). It can also refer to the total process of transporting and exchanging oxygen and carbon dioxide between the environment and the cell in the process of generating energy. Hence, terms exist for internal respiration (exchange of blood gases between the cell-extracellular fluid boundary) and external respiration (exchange at the alveolar-capillary boundary) to distinguish individual steps in the process. This term is often

used interchangeably with ventilation which is really only one aspect of respiration (see ventilation). Cellular respiration restricted to the aerobic process represents intercellular exchange of oxygen and carbon dioxide (producing as well energy and water).

**Sensitivity analysis** A study of how the variation in the parameters of a mathematical model will impact a particular measured state variable.

**Shunt (right-to-left)** Portion of blood flow bypassing the lung unit, representing a perfused but non-ventilated gas exchange unit. The shunt brings venous blood with high CO<sub>2</sub> tension to the arterial blood, hence elevating arterial CO<sub>2</sub> tension.

**Sit-to-stand** A physiological stress test (similar to head-up tilt) often used in the clinic to test the cardiovascular control system. During sit-to-stand test clinicians often measure dynamics (beat-to-beat) values for blood pressure, heart rate, blood flow, and quantities related to respiration including expiratory concentration of O<sub>2</sub> and CO<sub>2</sub>, as well as airflow.

**Sleep apnea** Pathological state characterized by cessation of breathing which occurs repetitively during sleep.

**Subset selection** Determination of a subset of model parameters that can be estimated reliably from experimental data.

**Sympathetic regulation** A part of the autonomic nervous system. It is activated via the baroreceptors and function via regulation of noradrenaline (or norepinephrine). In the cardiovascular system, sympathetic regulation impact heart rate, cardiac contractility, and vascular tone. Regulation of these quantities is mediated by the ganglionic nervous system, and it typically takes 5–10 s from the sensed change in blood pressure to the actual control of the effector organs.

**Transcranial Doppler** A test that measures the velocity of blood flow through the brain's blood vessels. Typically, flow is measured in the middle cerebral arteries, though the test also allows for measurement in anterior and posterior cerebral arteries.

**Unscented transformation** A practical method to estimate the statistics of a random variable undergoing a nonlinear transformation.

**Vascular tone** This refers to the degree of constriction experienced by a blood vessel relative to its maximally dilated state. All arteries and under basal conditions exhibit some degree of smooth muscle contraction that determines the diameter, and hence tone, of the vessel.

**Ventilation** The movement of air into and out of the lungs (the process of breathing). Minute ventilation is a measure in liters per minute. Tidal volume is a single inhalation or exhalation measured in liters per breath. Compare to the term Respiration.

# Index

- acetylcholine, 187
- acid-base, 141
- algorithm
  - EKF, 79
  - expectation maximization, 55
  - parameter estimation UKF, 82
  - recursive least-squares, 83
  - subset selection, 35, 51, 199
  - UKF, 81
- asymptotic standard error, 48
- autonomic regulatory system, 192
- autoregulation, 55
  
- baroreflex, 215
  - firing rate, 186
  - mechanisms, 185
- biomarkers, 184
- blood flow resistance, 190
- blood gases, 133
  - partial pressures, 134
  - storage capacity, 134
  - and ventilation, 122
- blood pressure
  - tissue, 188
  - venous, 220
  - weighted mean, 185
- blood volume
  - stressed volume, 189, 216
  - unstressed volume, 189, 215, 216, 222
  - mobilization, 216
- brain tissue
  - and respiration, 125, 133
  
- capacitance, 217
- carbon dioxide
  - and respiration, 133
  
- carbon dioxide reserve, 146
- cardiac output, 220
  - and blood gases, 122
- cardiovascular control
  - of cardiac contractility, 193
  - of peripheral resistance, 193
  - short term, 215
  - unstressed volume, 221
  - of vascular tone, 193
- cardiovascular system
  - compartment model, 189
  - data, 182, 222
- central chemoreceptors, 136
- cerebral blood flow, 147
  - regulation, 147
- chemoreflex, 91, 122, 144
- Cheyne–Stoke breathing, 100
- classical sensitivity analysis, 236
- closed loop model, *see* model, closed loop
- coefficient of variation, 50
- compliance, 189, 217
- congestive heart failure, 124
- control
  - cardiovascular, *see* cardiovascular control
  - chemoreflex, 135, 144
  - loop gain
    - chemoreflex, 124, 146
  - respiratory, *see* respiratory control
  - short term (in cardiovascular control), 215
  - unstressed volume, 221
- covariance learning
  - Hebbian feedback, 97
  
- design
  - criterion, 16
  - D-optimal, 16

- E-optimal, 16
- SE-optimal, 16
- diaphragm movement, 188
- elastance
  - left ventricular, 190
  - model, *see* model, ventricular elastance
  - ventricular elastance
    - maximum, 191
    - minimum, 191
- EPCA, 108
- exercise hyperpnea, 91
- experimental design, 16
- fainting, 207
- Fisher information matrix, 12, 48
- forward problem, 76
- gradient based optimization, 201
- gravity and blood flow, 192
- greatest integer function, 108
- head-up tilt and heart rate regulation, 203
- heart as a pump, 190
- heart rate, 185
  - modeling, *see* model, heart rate
  - potential, 187
  - regulation
    - and age, 201
    - and hypertension, 201
    - and normotensives, 201
- heart valve modeling, 191
- homeostasis, 90
- hypovolemia
  - central, 216
- identifiability
  - local, 11
  - of parameters, 11
- ill-posedness, 76
- in silico investigations, 185
- instability, 77
- integration, 92, 93
- inverse problem, 76, 195
- kalman filter, 14, 77, 78, 200
  - dual, 84–86
  - extended, 78
  - joint filter, 83
  - unscented, 78, 81
- least squares
  - cost, 110, 188
  - error, 192
  - estimator, 11, 46
  - least squares problem, 200
  - residual, 188, 192
- levenberg-Marquardt method, 201
- limit cycle, 101
- linear-quadratic regulator problem, 55
- lower body negative pressure, 216, 220
- mass balance, 218, 219
- measurement
  - autocorrelated, 10, 17
  - error, 10, 46
  - noise, 10
  - process, 10
- model
  - autonomic regulation, 192
  - baroreflex, 221
  - based analysis, 184
  - baroreflex regulation, 182, 184, 193
  - black box, 123
  - canonical, 182
  - cardiac output, 220
  - cardiovascular system, 189
  - cerebral autoregulation, 193
  - chemoreflex, 148
    - steady state, 144
  - closed loop, 184
  - compartment, 125, 189, 218
  - descriptive, 8
  - explanatory, 8
  - gray-box, 38
  - heart as pump, 190
  - heart rate
    - closed loop, 203
    - open loop, 201
  - heart valves, 191
  - identifiability
    - a posteriori, 237
    - a priori, 237
  - identification, 224
  - input–output, 123, 137, 139
  - multiscale, 184
  - nonlinear spring, 84, 85
  - open loop, 184, 185
  - output, 9
  - plasma-interstitial fluid exchange, 218
  - reduced, 122
  - reduced-order, 37
  - respiratory control, 106, 122
  - statistical, 10, 45, 46

- validation, 183, 195, 237
- ventricular elastance, 191
- modeling impact of gravity, 192
- modeling steady state blood flow, 192
- modeling with data, 182
- multiscale modeling, 91
  
- noradrenaline, 187
- numerical approximation, 108
  
- observations, 46
- Ohm's law for blood flow, 190
- optimization methods, 110, 200
- orthostasis
  - orthostatic stress, 23, 216
- output
  - measurable, 9, 45
- oxygen
  - and respiration, 133
  
- parameter
  - admissible, 45
  - correlations, 199
  - estimate, 11
    - consistent, 12
  - identifiability, 111, 200
  - identification, 11, 182
  - nominal, 10, 45
  - redundancy, 13
  - sensitivity, *see* sensitivity, parameter
  - true, 10, 45
- parameter estimation, 11, 77, 82, 109, 182, 195
  - chemoreflex, 140
  - methods, 200
  - patient specific, 122
  - via optimization, 183
- parasympathetic outflow, 185, 186
- periodic breathing, 122
  - and sleep, 124
- peripheral chemosensors, 136
- pH
  - kidney, 134
  - relation to  $\text{CO}_2$ , 134
  - respiratory control, 134
- postural change
  - sit-to-stand, 181
  
- QR decomposition
  - and subset selection, 35, 199
  
- rebreathing, 137
- reductionism, 90, 93
- regulation
  - cerebral blood flow, 147
  - chemoreflex, 146
  - metabolic regulation, 194
  - myogenic regulation, 194
  - neurogenic regulation, 194
- resistance
  - vascular, 216
- respiration
  - and altitude, 144
  - blood gases, 106, 134
  - and blood pressure, 188
  - chemoreflex, 106, 135
    - stability, 146
  - exercise, 135
- respiratory control, 105
  - optimization, 91, 95
  - reflex model, 95
  - stability, 146
  - stability and congestive heart failure, 124
  - ventilation, 123
- respiratory cost function, 96
- respiratory system
  - control overview, 133
  - data, 137, 139
  
- sampling distribution, 47
- sampling times, 10, 45
- selection score, 50
- sensitivity, 67
  - parameter, 183
  - identifiability, 236
  - sensitivity ranking, 197
- sensitivity analysis, 86, 195
  - generalized sensitivity, 236
  - via finite differences, 197
- sensitivity function, 13
  - classical, 14
  - generalized, 15
- sensitivity matrix, 13, 47, 48
  - generalized, 15
  - normalized, 14
- simulation, 23
- sit-to-stand and heart rate regulation, 203
- sleep, 142
  - NREM, 126
- sleep apnea, 122, 125
  - central, 122
  - obstructive, 122
- sleep state, 131

- stability
  - chemoreflex, 146
- standard error
  - asymptotic, 16
- stressed volume, *see* blood volume, stressed
- strong ion difference, 134
- subset selection, 32, 35, 86, 198, 236
  - algorithm, 35, 51, 199
  - error bound for singular values, 199
  - and QR decomposition, 35, 199
- sympathetic outflow, 185, 186
- syncope, 182, 207
  
- tilt
  - head up, 23, 181, 216, 220
- transcranial Doppler ultrasound, 181
- transport delay, 106
  
- unscented transform, 78, 80
- unstressed volume, *see* blood volume, unstressed
  
- validity
  - domain of, 8
- vascular capacitance, *see* capacitance
- Vascular compliance, *see* compliance
- ventilation
  - and blood gases, 123
  - and chemoreflex, 137
  - end-tidal, 137
  - and exercise, 135
  - feedback control, 137
  - hypoventilation, 126
  - response, 123
- ventilation function, 106
  - control gain, 106



Edited by J.-M. Morel, B. Teissier; P.K. Maini

**Editorial Policy** (for Multi-Author Publications: Summer Schools / Intensive Courses)

1. Lecture Notes aim to report new developments in all areas of mathematics and their applications - quickly, informally and at a high level. Mathematical texts analysing new developments in modelling and numerical simulation are welcome. Manuscripts should be reasonably selfcontained and rounded off. Thus they may, and often will, present not only results of the author but also related work by other people. They should provide sufficient motivation, examples and applications. There should also be an introduction making the text comprehensible to a wider audience. This clearly distinguishes Lecture Notes from journal articles or technical reports which normally are very concise. Articles intended for a journal but too long to be accepted by most journals, usually do not have this "lecture notes" character.

2. In general SUMMER SCHOOLS and other similar INTENSIVE COURSES are held to present mathematical topics that are close to the frontiers of recent research to an audience at the beginning or intermediate graduate level, who may want to continue with this area of work, for a thesis or later. This makes demands on the didactic aspects of the presentation. Because the subjects of such schools are advanced, there often exists no textbook, and so ideally, the publication resulting from such a school could be a first approximation to such a textbook. Usually several authors are involved in the writing, so it is not always simple to obtain a unified approach to the presentation.

For prospective publication in LNM, the resulting manuscript should not be just a collection of course notes, each of which has been developed by an individual author with little or no coordination with the others, and with little or no common concept. The subject matter should dictate the structure of the book, and the authorship of each part or chapter should take secondary importance. Of course the choice of authors is crucial to the quality of the material at the school and in the book, and the intention here is not to belittle their impact, but simply to say that the book should be planned to be written by these authors jointly, and not just assembled as a result of what these authors happen to submit.

This represents considerable preparatory work (as it is imperative to ensure that the authors know these criteria before they invest work on a manuscript), and also considerable editing work afterwards, to get the book into final shape. Still it is the form that holds the most promise of a successful book that will be used by its intended audience, rather than yet another volume of proceedings for the library shelf.

3. Manuscripts should be submitted either online at [www.editorialmanager.com/lnm/](http://www.editorialmanager.com/lnm/) to Springer's mathematics editorial, or to one of the series editors. Volume editors are expected to arrange for the refereeing, to the usual scientific standards, of the individual contributions. If the resulting reports can be forwarded to us (series editors or Springer) this is very helpful. If no reports are forwarded or if other questions remain unclear in respect of homogeneity etc, the series editors may wish to consult external referees for an overall evaluation of the volume. A final decision to publish can be made only on the basis of the complete manuscript; however a preliminary decision can be based on a pre-final or incomplete manuscript. The strict minimum amount of material that will be considered should include a detailed outline describing the planned contents of each chapter.

Volume editors and authors should be aware that incomplete or insufficiently close to final manuscripts almost always result in longer evaluation times. They should also be aware that parallel submission of their manuscript to another publisher while under consideration for LNM will in general lead to immediate rejection.

4. Manuscripts should in general be submitted in English. Final manuscripts should contain at least 100 pages of mathematical text and should always include
  - a general table of contents;
  - an informative introduction, with adequate motivation and perhaps some historical remarks: it should be accessible to a reader not intimately familiar with the topic treated;
  - a global subject index: as a rule this is genuinely helpful for the reader.

Lecture Notes volumes are, as a rule, printed digitally from the authors' files. We strongly recommend that all contributions in a volume be written in the same LaTeX version, preferably LaTeX2e. To ensure best results, authors are asked to use the LaTeX2e style files available from Springer's web-server at

<ftp://ftp.springer.de/pub/tex/latex/svmonot1/> (for monographs) and

<ftp://ftp.springer.de/pub/tex/latex/svmultt1/> (for summer schools/tutorials).

Additional technical instructions, if necessary, are available on request from:

[lnm@springer.com](mailto:lnm@springer.com).

5. Careful preparation of the manuscripts will help keep production time short besides ensuring satisfactory appearance of the finished book in print and online. After acceptance of the manuscript authors will be asked to prepare the final LaTeX source files and also the corresponding dvi-, pdf- or zipped ps-file. The LaTeX source files are essential for producing the full-text online version of the book. For the existing online volumes of LNM see:

<http://www.springerlink.com/openurl.asp?genre=journal&issn=0075-8434>.

The actual production of a Lecture Notes volume takes approximately 12 weeks.

6. Volume editors receive a total of 50 free copies of their volume to be shared with the authors, but no royalties. They and the authors are entitled to a discount of 33.3 % on the price of Springer books purchased for their personal use, if ordering directly from Springer.
7. Commitment to publish is made by letter of intent rather than by signing a formal contract. Springer-Verlag secures the copyright for each volume. Authors are free to reuse material contained in their LNM volumes in later publications: a brief written (or e-mail) request for formal permission is sufficient.

#### **Addresses:**

Professor J.-M. Morel, CMLA,  
École Normale Supérieure de Cachan,  
61 Avenue du Président Wilson, 94235 Cachan Cedex, France  
E-mail: [morel@cmla.ens-cachan.fr](mailto:morel@cmla.ens-cachan.fr)

Professor B. Teissier, Institut Mathématique de Jussieu,  
UMR 7586 du CNRS, Équipe "Géométrie et Dynamique",  
175 rue du Chevaleret,  
75013 Paris, France  
E-mail: [teissier@math.jussieu.fr](mailto:teissier@math.jussieu.fr)

*For the "Mathematical Biosciences Subseries" of LNM:*

Professor P. K. Maini, Center for Mathematical Biology,  
Mathematical Institute, 24-29 St Giles,  
Oxford OX1 3LP, UK  
E-mail : [maini@maths.ox.ac.uk](mailto:maini@maths.ox.ac.uk)

Springer, Mathematics Editorial I,  
Tiergartenstr. 17,  
69121 Heidelberg, Germany,  
Tel.: +49 (6221) 4876-8259  
Fax: +49 (6221) 4876-8259  
E-mail: [lnm@springer.com](mailto:lnm@springer.com)