STRUCTURAL CORRELATION METHOD FOR PRACTICAL ESTIMATION OF PATIENT SPECIFIC PARAMETERS IN HEART RATE REGULATION

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ABSTRACT

Numerous mathematical models have been proposed for prediction of baroreflex regulation of heart rate. Most models have been designed to provide qualitative predictions of the phenomena, though some recent models have been developed to predict observed data. In this study we show how sensitivity and correlation analysis can be used for model reduction and for obtaining a set of identifiable parameters that can be estimated reliably given a model and an associated set of data. We show that the model developed by Bugenhagen et al. to predict heart rate dynamics in the Dahl SS rat can be simplified significantly, without loss of its ability to predict measured data.

Keywords: Parameter estimation; Inverse problems; Model reduction; Subset selection; Simulation and modeling; Non-linear heart rate model; Patient specific modelling.

1. INTRODUCTION

Most models (including the one analysed here) have been developed with the aim of estimating dynamics of the system studied. Often models are developed in steps with the aim of including all known properties, rather than with the aim of obtaining the simplest self-contained model. The former is essential for gaining understanding of how various mechanical or physical properties impact the system dynamics, but may not be practical if the objective is to study how model parameters change within and between groups of subjects. For the latter, a simpler self-contained model may be better. This type of model often has fewer states and parameters. Estimation of reliable model parameters requires that sufficient data is available to identify all model parameters. Typically that is not the case, since experimental data often is sparse since they may be difficult and/or expensive to obtain. Consequently, as discussed in previous studies (Pope et al. 2009, Olufsen and Ottesen 2012) only a subset of parameters may be identifiable. In this study we show how sensitivity analysis and correlation analysis can be used for identifying model redundancies, which in turn can be used for model reduction. Furthermore, (as in previous studies) we show how reliable parameters can be estimated in a reduced model.

Based on (Houk et al. 1966, Scrinivasan-Nudelman 1972, Hasan 1983, Alfrey 1987, Ottesen 1997, Olufsen et al. 2006, Ottesen and Olufsen 2011) Bugenhagen et al. [2010] presented a nonlinear differential equations model developed to predict baroreflex regulation of heart rate as a function of blood pressure for Dahl SS rats. This model contains complex nonlinear dynamics and a large number of parameters. Data for this model is considered sparse since only one output quantity is measured (heart rate), though it is sampled at a high frequency. The model is complex since it contains nonlinear dynamics as well as several time scales including fast inter-beat dynamics and slow dynamics associated with baroreflex regulation. It contains more than 30 parameters characterizing all known properties of the system. The model is developed from first principles describing the underlying mechanisms, with model parameters representing physiological quantities including arterial wall deformation, deformation of the baroreceptor nerve-endings, firing of afferent neurons, prediction of neurotransmitter dynamics (acetylcholine and noradrenaline) and the impact on heart rate. Although, the model was able to predict measured data no attempts were made to simplify the model or to analyse the reliability of the estimated parameters.

In this study we show how to simplify the heart rate model developed by Bugenhagen et al. [2010] by reducing the number of adjustable parameters. Then, for the reduced model, we demonstrate how to identify a subset of its parameters and estimate these so the model is able to predict measured heart rate.

2. MATHEMATICAL MODEL

In this section we first discuss concepts needed for prediction of sensitivities and correlations; second we apply these methods to analyse the heart rate model developed by Bugenhagen et al. [2010].

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Sensitivity, correlation analysis, and parameter estimation

To predict sensitivities and pairwise correlations, we assume that the model can be formulated as a system of nonlinear differential equations of the form

$$\frac{dx}{dt} = f(t, x; \theta),$$

where $f: \mathbb{R}^{1+n+q} \to \mathbb{R}^n$, $t \in \mathbb{R}$ denotes time, $x \in \mathbb{R}^n$ denotes the state vector, and $\theta \in \mathbb{R}^q$ denotes he parameter vector. Associated with the states we assume an output vector $y \in \mathbb{R}^m$ corresponding to the available data (heart rate). We assume that this output can be computed algebraically as a function of the time t, the states x, and the model parameters θ, i.e.

$$y = g(t, x; \theta),$$

where $g: \mathbb{R}^{1+n+q} \to \mathbb{R}^m$. By construction the model output y is associated with data Y sampled at times t_i, where the sampling rate may vary between output components.

Sensitivities predict how much the model output changes with a change in the parameters. Classically (Frank 1978), the sensitivity matrix S of order $n \times l \times q$ (where l is the sampling cardinality) is defined by

$$S = \frac{\partial y}{\partial \theta}.$$

If model parameters vary significantly in magnitude, it may be advantageous to use relative sensitivities defined by

$$\tilde{S} = \frac{\partial y}{\partial \theta} \frac{\theta}{y}, \quad y \neq 0.$$

Rank of the sensitivities (either classical or relative) can be computed as

$$S_R = \|S\|_2.$$

Pairwise parameter correlations can be predicted from the sensitivity matrix using the structured analysis discussed in (Olufsen and Ottesen 2012). As a point of departure, this method uses the model Hessian (a positive definite symmetric matrix sometimes denoted the Fisher information matrix, (Cintron-Arias et al. 2009)), which for problems with constant variance σ^2, can be defined by $\mathcal{H} = \sigma^{-2} S^T S$ (Yue et al. 2006). Using $\mathcal{H}$, the correlation matrix c can be computed from the covariance matrix $C = \mathcal{H}^{-1}$ as

$$c_{i,j} = \frac{C_{i,j}}{C_{i,i} C_{j,j}}.$$

Notice that the matrix C only exists if the determinant of is $\mathcal{H}$ is non-vanishing. The matrix c is symmetric with elements $|c_{i,j}| \leq 1$. Parameter pairs (i, j) are considered correlated, if $|c_{i,j}| \geq \gamma$ for some value of γ. We denote such pairs as practically correlated parameters.

In this study we used the following structured approach to identify a set of sensitive and uncorrelated parameters. Assuming $\mathcal{H}$ is non-singular,

1. Compute the correlation matrix c and identify all correlated parameter pairs, i.e., identify parameter pairs for which $|c_{i,j}| \geq \gamma$.
2. Sort correlated parameters according to their sensitivity. List all parameters ordered from the least to the most sensitive.
3. Remove the least sensitive correlated parameter from θ and recompute c for the reduced parameter set (this set can easily be done by deleting the corresponding column of S). The parameters removed from θ should be kept fixed at their *a priori* value.
4. Continue from 1 until $|c_{i,j}| < \gamma$ for all (i, j).

For some models, the Hessian is singular. This follows if two or more parameters are conditionally identifiable (perfectly correlated) giving rise to redundancy. For this case, it is often possible to reduce the model eliminating either a parameter or an equation. Moreover, some equations may be superfluous in the sense that they hardly influence the model output. Thus we may perform an additional model reduction by removing or simplifying such model equations. Model reduction as part of the identification of a set of sensitive and uncorrelated parameters is an iterative process alternating between numerical and analytical considerations.

Once a reduced model and a set of identifiable parameters have been identified, parameter estimation methods can be employed to estimate the identifiable parameters. Assuming that the error between the model output and data are normally distributed, parameters can be estimated via solution of the inverse problem. In this study, parameters are estimated using the Levenberg-Marquart gradient-based method, which estimates parameters that minimize the least squares error between computed and measured values of the model output (Kelley 1999).

Heart rate model

Heart rate is one of the most important quantities controlled by the body to maintain homeostasis. The control of heart rate is mainly achieved by the autonomic nervous system involving a number of subsystems that operate on several time and length scales. One of the major contributors to autonomic regulation of heart rate is the baroreflex system, which operates on a fast time-scale (seconds). Baroreflex control consists of three parts: an affector part, a control center, and an effector part (Ottesen 1997, Ottesen and Olufsen 2011). The firing rate of the afferent baroreceptor neurons is modulated by changes in the viscoelastic stretch of the nerve-endings terminating in the arterial wall of the aorta and carotid sinuses. It is assumed that the deformation of the nerve-endings is modulated relative to the deformation of the arterial wall, which is imposed via changes in arterial pressure. The afferent neurons terminate in the nucleus solitary tract (NTS) within the medulla. The effector part consists of sympathetic and parasympathetic outflows, generated in NTS. The parasympathetic outflow travel along the vagal nerve, whereas sympathetic outflow travel via a network of interconnected neurons.

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The main neurotransmitters involved with modulating heart rate regulation are acetylcholine, which is released by the vagal nerves, and noradrenaline released from the postganglionic sympathetic nerves. The model components are summarized in Figure 1.
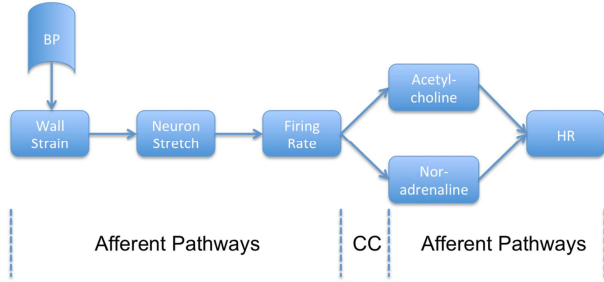

Figure. 1. Model components. CC denotes the control center, the nucleus solitary tract, which integrates all sensory inputs.

It is commonly assumed that the wall strain can be defined as

$$\varepsilon_w = \frac{R - R_0}{R_0},$$

which can be rewritten as

$$A = \pi R_0^2 (\varepsilon_w + 1)^2.$$

The approach suggested by Srinivasen and Nudelman [1972] is adopted assuming that stress is proportional to pressure. The latter is reasonable for a thin-walled tube (Valdez-Jasso, 2011). Bugenhagen et al. [2010] assumed a first order transient toward such static relation predicting the change in area A as

$$\frac{dA}{dt} = \frac{1}{B_w}\left(p - \frac{\sqrt{A/\pi} - R_0}{c_w}\right),$$

where $A_0 = \pi R_0^2$ and $A = \pi R^2$. In contrast to Bugenhagen [2011] these equations may be combined in a single differential equation for that relates wall stretch and pressure

$$\frac{d\varepsilon_w}{dt} = \frac{1}{2\pi R_0^2 B_w}\frac{1}{\varepsilon_w + 1}\left(p - \frac{R_0 \varepsilon_w}{c_w}\right).$$

Note $p(t_i)$ is obtained from the pressure data.

Using the idea originally put forward by Houk et al. [1966] and Hasan [1983] and later used by Alfrey [1987] inspiring Bugenhagen et al. [2010] the stretch of the baroreceptor nerve endings can be predicted assuming that the cells embedded in the wall respond viscoelasticly to the vessel strain ε_w. The deformation of the baroreceptor nerve endings is predicted using Fung's (Fung, 1993), mechanical model with three Voigt bodies (see Figure 2) in series, given by

$$\frac{d\varepsilon_1}{dt} = \frac{K_n(\varepsilon_w - \varepsilon_1) - K_1(\varepsilon_1 - \varepsilon_2)}{B_1} - \frac{d\varepsilon_2}{dt}$$

$$\frac{d\varepsilon_2}{dt} = \frac{K_1(\varepsilon_1 - \varepsilon_2) - K_2(\varepsilon_2 - \varepsilon_3)}{B_1 + B_2} + B_1\frac{d\varepsilon_1}{dt} + B_2\frac{d\varepsilon_3}{dt}$$

$$\frac{d\varepsilon_3}{dt} = \frac{K_2(\varepsilon_2 - \varepsilon_3) - K_3\varepsilon_3 + B_2\frac{d\varepsilon_2}{dt}}{B_2 + B_3}.$$
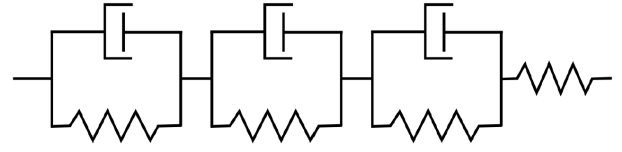

Figure 2: Three Voigt bodies in series. K_i denotes the spring constants and B_i the dashpots characterizing the viscoelastic cell and wall components. Finally, the spring in series with the dashpots is denoted by K_n.

For clarity these equations are rewritten in explicit form as

$$\frac{d\varepsilon_1}{dt} = -(a + \alpha_1 + \alpha_2 + \alpha_3)\varepsilon_1 + (a - b)\varepsilon_2$$
$$+ (b - c)\varepsilon_3 + (\alpha_1 + \alpha_2 + \alpha_3)\varepsilon_w$$

$$\frac{d\varepsilon_2}{dt} = -(\alpha_2 + \alpha_3)\varepsilon_1 - b\varepsilon_2 + (b - c)\varepsilon_3$$
$$+ (\alpha_2 + \alpha_3)\varepsilon_w$$

$$\frac{d\varepsilon_3}{dt} = -\alpha_3\varepsilon_1 - c\varepsilon_3 + \alpha_3\varepsilon_w$$

where

$$a = \frac{K_1}{B_1}, \qquad b = \frac{K_2}{B_2}, \qquad c = \frac{K_3}{B_3}$$
$$\alpha_1 = \frac{K_n}{B_1}, \qquad \alpha_2 = \frac{K_n}{B_2}, \qquad \alpha_3 = \frac{K_n}{B_3}.$$

Notice that the rewritten equation involves six parameters, whereas the original equations in Bugenhagen [2011] involved 7 parameters. By combining two algebraic equations stated in (Bugenhagen et al. 2010) the firing rate model can be written as

$$f = M(\varepsilon_w - \varepsilon_1).$$

The afferent firing rate f is integrated in the NTS, where the sympathetic T_S and the parasympathetic T_P outflows are generated. We emphasize that the representation and interpretation of the rest of the model deviate slightly from what Bugenhagen [2011] did. Assuming saturation, these have been described using Hill functions as (Olufsen et al. 2006, Ottesen and Olufsen 2011)

$$T_S = T_{SM} - (T_{SM} - T_{Sm})\frac{f^\eta}{f^\eta + f_S^\eta}$$

$$T_P = T_{Pm} + (T_{PM} - T_{Pm})\frac{f^\xi}{f^\xi + f_P^\xi},$$

where subscript m refers to the minimum and subscript M refers to the maximum outflows, whereas η and ξ are constants predicting the steepness of the sigmoid. The next step involves prediction of the concentration of neurotransmitters acetylcholine C_A and C_N noradrenaline, which can be obtained from

$$\frac{dC_A}{dt} = -\frac{C_A}{\tau_A} + q_P T_P$$
$$\frac{dC_N}{dt} = -\frac{C_N}{\tau_N} + q_S T_S,$$

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where q_i and τ_i are time scales for build-up and decay of the neurotransmitter concentrations. Changes in the concentration of neurotransmitters impact the ionic stimulation of the heart. Acetylcholine binds to muscarinic receptors and noradrenaline binds to β-receptors controlling ion-channels. At least two channels pathways are affected in response to acetylcholine a slow sodium channel pathway and a fast potassium channel pathway, while noradrenaline mainly is associated with slower potassium and calcium channel pathways (Pyetan et al 2003, DiFrancesco 2006, Lyashkov et al 2009, Vinogradova TM and Lakatta 2009). In general about 75% of available acetylcholine stimulates the fast channel pathways while about 25% stimulates the slower channel pathways. For Noradrenaline, the full amount contributes to stimulating slower channel pathways. Common for all neurotransmitters stimulating the system is that the effect saturate at high concentrations. The actual complexity of ion-channels taking place in building up an action potential and herby regulating the heart rate is huge. Thus we simplify this complex mechanism by assuming a quasi-steady state of the occupied muscarinic and β-receptors and lumping all subsequent pathways into three hypothetical substances. For details see appendix A. Consequently, for noradrenaline we have

$$\frac{dC_{NS}}{dt} = \frac{1}{\tau_{NS}}\left(\frac{C_N^2}{C_N^2 + K_N^2} - C_{NS}\right)$$

while for acetylcholine we get

$$\frac{dC_{AF}}{dt} = \frac{1}{\tau_{AF}}\left(\mu\frac{C_A^2}{C_A^2 + K_A^2} - C_{AF}\right)$$
$$\frac{dC_{AS}}{dt} = \frac{1}{\tau_{AS}}\left((1-\mu)\frac{C_{AS}^2}{C_{AS}^2 + K_A^2} - C_{AS}\right),$$

where τ_i are time-scales, F and S denote a fast and slow response (i.e., $\tau_{NS}, \tau_{AS} \gg \tau_{AF}$), μ is a weighting parameter, and K_i denotes half the max response. Assuming the fast cholinergic process is almost instantaneous, the first equation can be replaced by

$$C_{AF} = \mu\frac{C_A^2}{C_A^2 + K_{AF}^2}.$$

Assuming that fast and slow responses are additive, the overall contribution gives

$$C_{AT} = C_{AS} + C_{AF}, \quad C_{NT} = C_{NS}.$$

Finally, we computed heart rate as

$$h = h_0 + (h_M - h_0)C_{NT} - (h_0 - h_m)C_{AT}$$
$$- \frac{1}{h_0}(h_M - h_0)(h_0 - h_m)C_{NT}C_{AT},$$

where h_0 is the intrinsic heart rate, h_M and h_m denotes the maximal and minimal heart rate weighting, and the neurotransmitters are defined by C_{NT} and C_{AT}. In terms of the general theory outlined, $n = 8$ denotes the number of differential equations in the model. These are $x = (\varepsilon_w, \varepsilon_1, \varepsilon_2, \varepsilon_3, C_N, C_A, C_{NS}, C_{AS})$, where $m = 1$ denotes

the model output (heart rate), given by $y = h$. The model presented above has 30 parameters

$$\theta = (R_0, c_w, B_w, a, b, c, \alpha_1, \alpha_2, \alpha_3, M,$$
$$\eta, \xi, T_{Sm}, T_{SM}, T_{Pm}, T_{PM}, f_S, f_P, \tau_N, \tau_A, q_S, q_P,$$
$$\tau_{NS}, \tau_{AS}, K_N, K_A, \mu, h_0, h_m, h_M).$$

Model reduction and analysis

Sensitivity analysis (as defined by Frank [1978]) reveals that the sensitivity matrix $S = \partial h/\partial \theta$ is singular indicating that the model contains parameters that are perfectly correlated. Analysis of the equations reveals two correlations. First, the equation for ε_w can be simplified as

$$\frac{d\varepsilon_w}{dt} = \frac{p - K_{w1}\varepsilon_w}{K_{w2}(\varepsilon_w + 1)}$$

where $K_{w1} = R_0/c_w$ and $K_{w2} = 2\pi R_0^2 B_w$, i.e. c_w and B_w are conditionally identifiable with respect to R_0. Second, substituting the expression for f into the expresions for T_S and T_P shows that M is redundant. Thus the gain M may be incorporated into f_S and f_P, i.e. they are conditionally identifiable with respect to M. Hence this equation reduces to

$$f = \varepsilon_w - \varepsilon_{1.}$$

With these simplifications the model can be formulated using the following 28 parameters:

$$\theta = (K_{w1}, K_{w2}, a, b, c, \alpha_1, \alpha_2, \alpha_3,$$
$$\eta, \xi, T_{Sm}, T_{SM}, T_{Pm}, T_{PM}, f_S, f_P, \tau_N, \tau_A, q_S, q_P,$$
$$\tau_{NS}, \tau_{AS}, K_N, K_A, \mu, h_0, h_m, h_M).$$

We emphasize that the resulting reduced model has an non-singular Hessian in contrast to the former model.

3. RESULTS

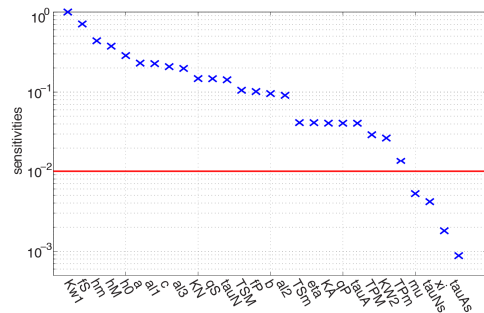For the reduced model, ranked sensitivities (see Figure 3) were calculated.

Figure 3: Sensitivity ranking, parameters below the horizontal line are considered insensitive.

Parameters $(\xi, \tau_{NS}, \tau_{AS}, \mu)$ with a sensitivity-norm lower than 0.01 were considered insensitive, and parameters (c, α_3) representing long time-scales compared to available data were kept at *a priori* values. Correlations among the remaining parameters were identified, leaving the following 17 parameters identifiable:

$$\theta = (K_{w1}, K_{w2}, a, b, \alpha_1, \alpha_2, f_S, f_P,$$
$$T_{Sm}, T_{SM}, T_{Pm}, T_{PM}, \tau_N, \tau_A, q_A, K_N, h_m).$$

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Table 1 compares parameter values from (Bugenhagen et al. 2010) with those used in the simplified model, and Figure 4 shows measured and optimized blood pressure and heart rate values.

Parameter	Bugenhagen	Simplified model
f_S	**0.125**[*]	**0.123**
f_P	**0.138**[*]	**0.133**
η	**15.2**	15.2
ξ	**23.3**	23.3
T_{Sm}	**0.487**	**0.635**
T_{SM}	**4.20**	**3.62**
T_{Pm}	**0.910**	**1.21**
T_{PM}	**2.31**	**2.10**
K_{w1}	267[#]	**180**
K_{w2}	2.56[#]	**1.89**
a	1.5[#]	**1.86**
b	0.375[#]	**0.364**
c	**0.0156**[#]	0.0156
α_1	1[#]	**0.710**
α_2	0.1[#]	**0.0856**
α_3	**0.0149**[#]	0.0149
τ_N	9.1	**4.78**
τ_A	0.2	**0.137**
q_N	0.11	0.110
q_A	5	**5.93**
K_N	1.12	**0.628**
K_A	0.65	0.650
τ_{Ns}	2.1	2.10
τ_{As}	2.5	2.50
γ	0.75	0.750
h_0	**347**	347
h_M	**648**	**1117**
h_m	**253**	253

Table 1: Comparison of parameter values from Bugenhagen et al. [2010] (left) with those obtained by the simplified model (right). Estimated (by optimization) parameters are marked in bold. Values marked by * are predicted to make Bugenhagen's formulation for T_S, T_P match our formulation. Values marked by # are calculated to convert the equations in Bugenhagen to formulation used in the simplified model.

4. CONCLUSION

In this study we used sensitivity and structural correlation analysis to simplify an existing model for heart rate regulation developed by Bugenhagen et al. [2010]. We also showed how to identify a subset of parameters that can be estimated given a model and a given set of experimental data. Results showed that the model contains several parameters that are not identifiable given the heart-rate data. If the objective is to estimate some of these parameters additional data from the same rat is needed.

APPENDIX A

Acetylcholine binds to muscarinic receptors and noradrenaline binds to β_1-receptors at the sinus node controlling the ion-channels of the cell membranes. The actual complexity of ion-channels, taking into account the building up of an action potential and subsequently
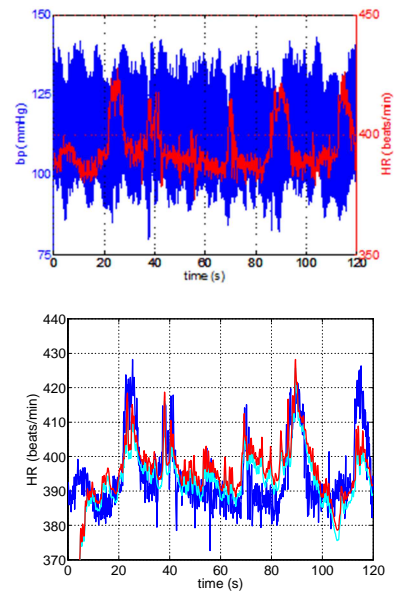

Figure 4. Top: Measured and predicted blood pressure (blue) and heart rate (red). Bottom: Measured (blue) and predicted (red and cyan) heart rate. The red trace shows results with the reduced model and cyan trace shows results from (Bugenhagen et al. 2010).

regulating heart rate is immense: At least six ion-channels are important for the generation of the action potential and hence for the heart rate, f-channels (sodium channels I_f), cholinergic calcium channels ($I_{K;ACh}$), non-transmitter dependent potassium channels (I_K), L-type (long lasting) calcium channels ($I_{Ca;L}$) T-type (transient) calcium channels ($I_{Ca;T}$), and calcium-sodium exchange channels (I_{NCX}) as illustrated in Figure 5. All of these ion-channels are regulated through (either inhibitory or stimulating) G-proteins: Acetylcholine binds to muscarinic receptors, down regulating cyclic AMP (cAMP) and phosphokinase A (PKA), which upregulates Na^+ (I_f) and down regulates K^+ ($I_{K;ACh}$) and Ca^{++} ($I_{Ca;L}$) whereas noradrenaline binds to β_1-receptors upregulating cAMP and PKA (Pyetan et al 2003, DiFrancesco 2006, Lyashkov et al 2009, Vinogradova TM and Lakatta 2009).
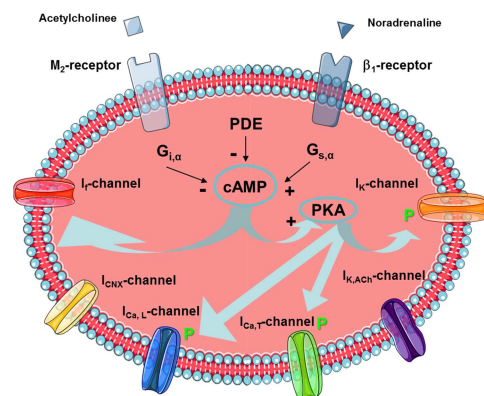

Figure 5. Ion-channels and pathways of greatest importance for the generation of the action potential and thus for the heart

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rate: f-channel (sodium channels I_f), cholinergic calcium channel ($I_{K;ACh}$), non-transmitter dependent potassium channel (I_K), L-type (long lasting) calcium channel ($I_{Ca;L}$) T-type (transient) calcium channel ($I_{Ca;T}$), calcium-sodium exchange channel (I_{NCX}), inhibitory G-protein (G_i), stimulating G-protein (G_s), muscarinic receptor (M_2), β_1-receptor, cyclic AMP (cAMP), phosphokinase A (PKA), and phosphodiesterase (PDE).

Common for all neurotransmitters stimulating such systems is that the effect saturate at high concentrations, which may be explained by simplifying the complex mechanism underlying it, e.g., by assuming a quasi-steady state for the occupied receptors. For simplicity we imagine that two molecules of the neural transmitter (C) binds to an receptor (R) forming an occupied receptor complex in a reversible reaction with rates c_+ and c_- and that the occupied receptor in addition may undergo another transition to the free state producing some substance (A) with rate c_1,

$$2C + R_{free} \underset{c_-}{\overset{c_+}{\rightleftharpoons}} R_{occ} \overset{c_1}{\to} R_{free} + A.$$
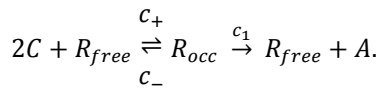
We also assume conservation of the receptor type, i.e.,

$$R_{free} + R_{occ} = R_0.$$

Hence the number of occupied receptor is govern by

$$\frac{dR_{occ}}{dt} = c_+ C^2 R_0 - (c_1 + c_- + c_+ C^2) R_{occ}.$$

In the quasi-steady state approximation this gives

$$R_{occ} = R_0 \frac{C^2}{C^2 + k_R^2},$$

where $k_R^2 = (c_1 + c_-)/c_+$. It is further assumed that the occupied receptors control the states of the ion-channels and thus the relevant intercellular pathways in building up the action potential. To omit this complexity we simply lump these path-ways into one or two substrates for each of the neurotransmitters, i.e., two for acetylcholine (C_{AF} or C_{AS}) and one for noradrenaline (C_{NS}), two channels are affected in response to acetylcholine a slow sodium channel and a fast potassium channel, while noradrenaline mainly is associated with slower channels. We assume that 75% of the occupied receptors stimulate the synthesis of the substance C_{AF} corresponding to the fast K^+-channels while about 25% stimulates the synthesis of the substance C_{AS} corresponding to the slower Na^+-channel. For noradrenaline, the full amount stimulates the synthesis of the substance C_{NT} corresponding to slow Na^+ and Ca^{++}-channels. Hence, for all three substances a fraction of the amount of occupied receptors serves as a production rate while the elimination are assumed proportional to the amount of the substance itself, thus the elimination rates are assumed constant (r),

$$\frac{dC_{xy}}{dt} = R_0 \left(\mu_{xy} \frac{C_x^2}{C_x^2 + k_R^2} - \frac{r}{R_0} C_{xy} \right),$$

where we use index $x = A, N$ (denoting acetylcholine and noradrenaline) and $y = F, S$ (denoting fast and slow

if necessary). Normalizing C_{xy} by r/R_0 and substituting $\tau_{xy} = 1/r$ gives

$$\frac{dC_{xy}}{dt} = \frac{1}{\tau_{xy}} \left(\mu_{xy} \frac{C_x^2}{C_x^2 + k_R^2} - C_{xy} \right).$$

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