Modelling and Simulation of Regional Cerebral Circulation

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Abstract— Regional cerebral perfusion pressure (rCPP) drives regional cerebral blood flow (rCBF) in the area surrounding stroke. The rCPP is a difference between the local inflow and outflow pressures, the latter being either venous or tissue pressure, whichever is higher. Therefore understanding of rCBF distribution after stroke requires creation of the unified approach reflecting rCBF and rCPP relationship.

We used hybrid systems simulation method based on the piece-linear aggregate (PLA) formalism in which integrators for differential equations are quantised into PLA models. We modelled rCBF by the modified Windkessel circulation model: we added variable resistance element, dependent on the external compression, and variable capacitance element, reflecting transmural pressure/volume relationship of the blood vessel, thus achieving ability to model regional compression of cerebral circulation. We demonstrated that modified Windkessel element can model phenomenon of rCPP reduction by local compression.

Index Simulation, Windkessel model, Hybrid Temporal-Spatial Simulation, Piece Linear Aggregates.

1 Introduction

Measurement of regional cerebral circulation has been carried out since 1940s with the use of diffusible inert gases (Kety, et al., 1948). That was followed by introduction of intravascular X-ray contrast media[1], intravascular radio- tracers[2], positron emission tomography (PET)[3], single-photon emission computed tomography (SPECT)[4], and magnetic resonance imaging (MRI), in particularly with intravascular contrast media[5]. These methods allow measurement of the important indicators of regional cerebral circulation: cerebral blood flow (CBF), cerebral vascular mean transit time (MTT), and cerebral blood volume (CBV), all of which can be measured by PET, while MTT and CBV can be measured by MRI with intravascular contrast media. However all these methods only allow visualizing three-dimensional distribution of blood flow and/or blood volume. Such images are the end result of the forces driving blood flow, yet these forces themselves remain hidden from the direct visualisation, and can be inferred only from the images obtained.

Visualization of flow is assumed to reflect distribution of vascular resistance. This may be oversimplification in cases where effective outflow pressure varies between the regions.

Description of vascular network requires presentation of three dimensional distribution of regional cerebro-vascular resistances (rCVR) and perfusion pressures (rCPP) as the determinants of regional cerebral blood flow: 
\[ rCBF=\text{rCPP/rCVR} \]
From there, correction of cerebral blood flow maldistribution requires determination if rCVR or rCPP is the primary cause of decreased flow. Then therapeutic maneuvers could be prioritized in the direction of re-canalization or loading condition adjustment.

Creating regional circulation model is the first step in solving the inverse problem -- reconstruction of rCPP and rCVR from ABP and CBF in time.

In order for image to reflect an underlying physiology, the image of circulation driving forces must be obtained. The primary blood flow driving force at regional and global level alike is perfusion pressure. At the regional level it has its own three-dimensional distribution, which might or might not mirror the three-dimensional distribution of flow. Capacity to visualize this three-dimensional distribution of regional perfusion pressures would add another dimension in diagnosis and treatment of cerebral circulation disturbances. Most recent success in model driven non-invasive blood pressure measurement intracraniial pressure points to the direction of how this might be accomplished. It would have to be imaging, driven by regional circulation model and its verification, combined with the continuous blood pressure monitoring. Essential step in such endeavour is simulation of regional cerebral circulation what is presented in this article.

We were first to introduce the use of nonlinear Starling resistor model to describe the effects of compartmental tissue pressure on regional cerebral perfusion pressure (rCPP) and regional cerebral blood flow (rCBF)[6]. Others tried to emulate this approach by using our steady state model with the source of alternating flow [7]. However such approach is erroneous when the dynamic flow is simplistically added to the steady state model: blood redistribution dynamics in this case should be accounted for by adding inductive and capacitive elements.

Starling resistor mimics vascular waterfall by assuming that local perfusion pressure is a difference between the inflow pressure and either compartmental tissue or venous
pressure, whichever is higher. This model was adequate to simulate steady state blood flow distribution between two or three compartments, but did not address complexity of the dynamics of blood redistribution through multiple networks. Moreover, depending on the initial conditions and dynamics of the transition, multiple solutions for blood flow distribution are possible. To address these problems, Starling resistor model had to be upgraded with the compliance and inductivity to simulate effects of inertia and effects of transmural pressure on the compartmental vascular volume.

2 Blood vessel model

We created a lumped model for blood vessel compartment (Fig. 1), containing variable Starling resistor, nonlinear capacitor, inductivity and additional resistors. In this model we simulated compartmental pressure by additional variable E.

2.1 Windkessel model

Windkessel model is widely used to simulate hemodynamic. Windkessel in German is translated as ‘air chamber’, and represents elastic reservoir, namely elastic arteries[8]. Arteries distend when blood pressure rises during systole and recoil when blood pressure falls during diastole. Therefore Windkessel element incorporates inductive, capacitive and resistive elements, yet it does not take into account fluctuations of blood volume and outflow resistance due to regional transmural pressure.

Standard Windkessel model incorporates 2, 3 or 4 elements (2-WM, 3-WM, 4-WM), 2-WM consists of parallel resistor and capacitance. 3-WM adds resistor in series. 4WM adds inductivity in series or parallel with additional resistor to 2-WM.

Our modification of Windkessel model incorporates inductivity L, nonlinear resistor R and nonlinear capacitor C (Fig. 1). We incorporated additional resistors R₁, R₂ and R₃ to simulate all classic configurations of Windkessel model (2-WM, 3-WM and both versions of 4_WM). Reduced model (2-WM) has L = 0, R₁ = R₂ = R₃ = 0.

\[ U_a, U_v \] simulate inflow and outflow pressure, furthermore difference between \( U_a \) and \( U_v \) is regional cerebral perfusion pressure (rCPP).

2.2 Starling resistor

We used nonlinear resistor \( R \) to describe effects of compartmental tissue pressure on the regional cerebral perfusion pressure (rCPP) and regional cerebral blood flow (rCBF)[6]. Starling resistor \( R \) depends on the external compression.

Starling resistor \( R \) is described by following equation:

\[
R(U_1, U_o, U_e) = \begin{cases} 
0, & U_o(U_1, U_o, U_e) = 0 \\
\infty, & U_o(U_1, U_o, U_e) \neq 0 \\
\frac{U_0(U_1 - U_o)}{U_1(U_1, U_o, U_e)}, & U_o(U_1, U_o, U_e) > 0, 
\end{cases}
\]

Where \( R_0 \) is selected minimum value of Starling resistance \( R \), when external pressure is equal zero, \( \land, \lor \) is AND, OR operators. \( U_1, U_o, U_e \) are inflow, outflow and external pressure respectively. Function \( U_o(U_1, U_o, U_e) \) describes transmural pressure of blood vessel (2):

\[
U_o(U_1, U_o, U_e) = (U_1 - U_o)H(U_1, U_e)H(U_o, U_e) + (U_1 - U_e)H(U_1, U_o)H(U_e, U_o)H(U_1, U_e) + H(U_e - U_o)H(U_o, U_e) + H(U_1, U_o)H(U_e, U_o)H(U_1, U_e).
\]

where \( H \) is the Heaviside function (3):

\[
H(x, y) = \begin{cases} 
0, & x - y < 0 \\
\frac{1}{2}, & x - y = 0 \\
1, & x - y > 0.
\end{cases}
\]

2.3 Nonlinear capacitance

Variable capacitance \( C \) of Windkessel model incorporates transmural pressure / volume relationship of the blood vessels, which generally has sigmoid, nonlinear form[6][8]. Variable capacitance \( C \) and electrical charge \( Q \) is described by (4) and (5), respectively:

\[
C(U_s) = \frac{Q_0 k e^{-k U_s}}{1 + e^{-k U_s}}.
\]

\[
Q(U_s) = \frac{Q_0}{1 + e^{-k U_s}}.
\]

where \( Q_0 \) represents maximal blood volume, capacitance \( C(U_s) \) is describing transmural pressure-blood volume relationship differential, \( k \) is slope constant. \( Q(U_s) \) is blood volume dependence on transmural pressure.
2.4 Physiological interpretation

Modified Starling resistor allows to simulate one of the most interesting and under-researched phenomenon of the cerebral blood flow circulation - its regional distribution. Blood flow distribution through the network of circulatory segments is determined not only by the regional resistances, but also by the local perfusion pressures (difference between inflow and tissue compartment pressures). Using variable resistance, Starling modification of Windkessel model allows simulation of local perfusion pressure distribution. The goal of such simulation is to obtain realistic regional blood flow and blood volume distribution models simulating effects of arterial, venous, and local tissue pressures, and allowing to correlate simulation results with rCBF/rCBV (regional cerebral blood flow and regional cerebral blood volume) maps from CT (computer tomography) or MR (magnetic resonance) angiograms with the intent to optimise rCPP after stroke.

3 Hybrid aggregate model

Cerebral blood flow is dynamic system that exhibits both continuous and discreet dynamit behaviour. For simulation of distribution of the blood flow between compartments we used hybrid systems simulation method based on PLA formalism [9].

PLA is a special case of automaton models. In the application of the PLA approach for system specification, the system is represented as a set of interacting piece-linear aggregates. The PLA is taken as an object defined by a set of states \( Z \), input signals \( X \), and output signals \( Y \). Behaviour of an aggregate is considered in a set of time moments \( t \in T \). States \( z \in Z \), input signals \( x \in X \), and output signals \( y \in Y \) are considered to be time functions. Transition and output operators, \( H \) and \( G \) correspondingly, must be known as well.

The state \( z \in Z \) of the piece-linear aggregate is \( z(t) = (v(t), z_x(t)) \), where \( v(t) \) is a discrete state component taking values on a countable set of values; and \( z_x(t) \) is a continuous component comprising of \( z_1(t), z_2(t), ..., z_{v_k}(t) \) coordinates.

When there are no inputs, an aggregate state changes as follows: \( v(t) = \text{const} \), \( \frac{dz_x(t)}{dt} = -a_v \), where \( a_v = (a_{v_1}, a_{v_2}, ..., a_{v_k}) \) is a constant vector.

The state of the aggregate can change in two cases only: when an input signal arrives at the aggregate or when a continuous component acquires a definite value.

. The set of events \( E \) which may take place in the aggregate is divided into two non-intersecting subsets \( E = E \cup E' \). The subset \( E' = \{e_1', e_2', ..., e_{N'} \} \) comprises classes of events (or simply events) \( e_i' \), \( i = 1, N \) resulting from the arrival of input signals from the set \( X = \{x_1, x_2, ..., x_N\} \). The class of events \( e_i' = [e_{ij}, j = \overline{1, N}] \), where \( e_{ij} \) is an event from the class of events \( e_i' \) taking place the j-th time since the moment \( t_0 \). The events from the subset \( E' \) are called external events. The events from the subset \( E'' = \{e_{1''}, e_{2''}, ..., e_{f'} \} \) are called internal events, where \( e_i'' = [e_{ij}, j = \overline{T, \infty}, i = \overline{1, f}] \) are the classes of the aggregate internal events. Here, \( f \) determines the number of operations taking place in the aggregate. The events in the set \( E'' \) indicate the end of the operations taking place in the aggregate.

For every class of events \( e_i'' \) from the subset \( E'' \), control sequences are specified \( \{z(i)\} \), where \( z(i) \) - the duration of the operation, which is followed by the event \( e_i'' \) as well as event counters \( \{r(e_i', t_m)\} \), \( r(e_i', t_m) \) is the number of events from the class \( e_i'' \) taken place in the time interval \( [t_0, t_m] \).

In order to determine start and end moments of operation, taking place in the aggregate the so-called control sums \( \{s(e_i'), t_m\} \), \( w(e_i', t_m) \) are introduced, where \( s(e_i', t_m) \) - the time moment of the start of operation followed by an event from the class \( e_i'' \). This time moment is indeterminate if the operation was not started; \( w(e_i', t_m) \) is the time moment of the end of the operation followed by the event from the class \( e_i'' \). In case of non-priority operations, the control sum \( w(e_i', t_m) \) is determined in the following way: \( w(e_i', t_m) = s(e_i', t_m) + \frac{x(t_m)}{r(e_i', t_m)} \). If at moment \( t_m \) an operation is taking place, which is followed by the event \( e_i' \); in the opposite case \( w(e_i', t_m) = \infty \). The infinity symbol (\( \infty \)) is used to denote the undefined values of the variables.

The continuous component of aggregate state \( z_v(t_m) = w(e_i', t_m), w(e_{i''}, t_m) \) comprises classes of events (or simply events) \( e_i'' \), \( i = 1, f \) resulting from the arrival of input signals from the set \( X = \{x_1, x_2, ..., x_N\} \). The class of events \( e_i'' = [e_{ij}, j = \overline{1, N}] \), where \( e_{ij} \) is an event from the class of events \( e_i'' \) taking place the j-th time since the moment \( t_0 \). The events from the subset \( E'' \) are called external events. The events from the subset \( E''' = \{e_{1''}, e_{2''}, ..., e_{f} \} \) are called internal events, where \( e_i''' = [e_{ij}, j = \overline{T, \infty}, i = \overline{1, f}] \) are the classes of the aggregate internal events. Here, \( f \) determines the number of operations taking place in the aggregate. The events in the set \( E''' \) indicate the end of the operations taking place in the aggregate.

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The operator $H$ states the new aggregate state.

$$z(t_{m+1}) = H[z(t_m), e_i], e_i \in E \cup E''.$$ 

The output signals $y_i$ from the set of output signals $Y = \{y_1, y_2, ..., y_m\}$ can be generated by an aggregate only at occurrence moments of events from the subsets $E'$ and $E''$. The operator $G$ determines the content of the output signals:

$$y = G[z(t_m), e_i], e_i \in E' \cup E'', y \in Y.$$ 

For hybrid aggregate model [9], in time intervals $t_m < t < t_{m+1}, v(t_m) = \text{const}$ and continuous coordinates model is described by the ordinary differential equations (ODE)

$$\frac{dz_c(t)}{dt} = f(t, z_c(t), x(t)).$$

For realization of hybrid aggregate model Quantized State System (QSS) method is used [10]. Fig. 2 illustrates simulation of ODE and each component is described using PLA formalism [9].

For creation of hybrid aggregate imitators we used PLASim simulation library [11]. The PLASim is an object-oriented library for discrete-event simulation of models created using aggregate formalism. The PLASim’s current version is written in C# for .NET Framework 4.0 and has packages that support random number generation, statistical collection, basic reporting with data visualization and discrete-event simulation. The development of a simulation model is based on sub-classing the SimulationModel class that provides the primary recurring actions within a simulation and event scheduling and handling. The user adds developed aggregates (model elements) based on subclassing the Aggregate class, to an instance of Model and then executes the simulation.

We expanded the PLA aggregate model simulation ability in such a way that at each discrete quantized time moment continuous coordinates value can be recalculated using derivative value of simulated function. We used this PLA expansion to create key component of the hybrid model - an integrator aggregate (Fig. 2).

Below is given modified QSS model integrator aggregate specification in PLA formalization language:

1. Set of input signals $X = \{S_1(t_m)\}$,

   where $S_1(t_m) \in R$ - function derivation, $S_1(t_m) = \frac{dX_1}{dt}$.

2. Set of output signals $Y = \{Q_j(t_m)\}_{j=1,...,r}$,

   where $Q_j(t_m)$ - quantized function value.

3. Set of external events $E' = \{e'_1\}$,

   where $e'_1$ - given a new derivation value.

4. Set of internal events $E'' = \{e''_1\}$,

   where $e''_1$ function reaches next quantized value.

5. Discrete component of state

   $$v(t_m) = \{X_1(t_m), x'_1(t_m), j_1(t_m)\},$$

   where $X_1(t_m) \in R$ - calculated function;

   $$x'_1(t_m) \in R - \text{derivation of function};$$

   $$j_1(t_m) \in Z - \text{number of quantized function value}.$$

6. Continuous part of state

   $$z_v(t_m) = \{w(e''_1, t_m)\},$$

   $w(e''_1, t_m)$ - time point of next internal event,

   $$w(e''_1, t_m) = \begin{cases} < \infty, x'_1(t_m) \neq 0; \\ \infty, \text{otherwise}. \end{cases}$$

7. Controlling sequences $e'_1 \mapsto \{\sigma_1\}$, $e''_1 \mapsto \{\sigma_2\}$

   where $\sigma_1$ and $\sigma_2$ time intervals after which the function $X_1$ will reach the next quantized value after external event, after internal event:

   $$\sigma_1 = \frac{(X_1(t_m) + (t_m - t_{m-1}) \cdot x'_1(t_{m-1})) - S_1(t_m)}{S_1(t_m)} > 0;$$

   $$\sigma_2 = \frac{(X_1(t_m) + (t_m - t_{m-1}) \cdot x'_1(t_{m-1})) - (Q_j(t_{m-1}) + e)}{S_1(t_m)} < 0;$$

   where $z$ – whole part of the number $z$,

   $e$ - hysteresis window,

   $\Delta Q$ - quantum value,

   $Q_1, Q_2 ... Q_r$ - grid of function discretization.

8. Initial state:

   $$v(t_0) = \{X_1(t_0), x'_1(t_0), j_1(f(X_1(t_0)))\};$$

   $$z_v(t_0) = \{t_0 + \sigma_2\}.$$

9. The transition and the output operators:

   $$H(e'_1(S_1(t_m))): \text{ came new value of the derivative}$$

   $$X_1(t_m) = X_1(t_{m-1}) + (t_m - t_{m-1}) \cdot x'_1(t_{m-1});$$

   $$x'_1(t_m) = S_1(t_m);$$

   $$j_1(t_m) = j_1(t_{m-1});$$

   $$w(e''_1, t_{m+1}) = t_m + \sigma_1.$$

10. $H(e''_1)$: \text{ achieved new quantified value of function } X_1/

    $$X_1(t_m) = X_1(t_{m-1}) + (t_m - t_{m-1}) \cdot x'_1(t_{m-1});$$

    $$x'_1(t_m) = x'_1(t_{m-1});$$

    $$j_1(t_m) = j_1(t_{m-1}) + \text{sgn}(x'_1(t_{m-1}));$$

    $$w(e''_1, t_{m+1}) = t_m + \sigma_2.$$
4 Blood vessel simulation

Blood vessel model (Fig. 1) is described by equations system, and then converted to PLA. According to the Kirchhoff law for electrical circuits [12]:

\[
\begin{align*}
    u(t) &= i_L(t)R_1 + L \frac{di_L(t)}{dt} + i_R(t)R + i_3(t)R_3, \\
    u(t) &= i_2(t)R_2 + \frac{1}{C} \int i_C(t) dt + i_3(t)R_3, \\
    0 &= i_L(t)R_1 + L \frac{di_L(t)}{dt} - i_2(t)R_2, \\
    0 &= i_R(t)R - \frac{1}{C} \int i_C(t) dt, \\
    i_L(t) + i_2(t) &= i_C(t) + i_R(t), \\
    i_C(t) + i_R(t) &= i_3(t).
\end{align*}
\]

Now we can rewrite (6) as hybrid equations system (7) using PLA formalism.

\[
\begin{align*}
    u_C(t) &= \frac{1}{C} \int \left( 1 + \frac{R_1}{R_2} \right) i_L(t) dt + \frac{L}{C \cdot R_2} i_L(t), \\
    i_L(t) &= \frac{1}{L} \left( u(t) - \left( R_1 + R_3 + \frac{R_1 R_2}{R_2} \right) i_C(t) - u_C(t) \right) dt.
\end{align*}
\]

Equations \( u_C(t) \) and \( u_{R_1}(t) \) on system (8) is used to imitate nonlinear elements \( R \) and \( C \) of Windkessel model.

\[
\begin{align*}
    u_C(t) &= R \cdot i_R(t), \\
    u_R(t) &= u_C(t) + \frac{R_3}{1 + \frac{R_3}{R_2}} \left( u(t) + i_L(t) \cdot \frac{u_C(t)}{R_2} \right), \\
    u_I(t) &= u_0(t) + u_C(t).
\end{align*}
\]

Below are simulation results of Windkessel model (Fig. 1) using nonlinear capacitor (4) and nonlinear resistor (1). To estimate model parameters we used arterial blood pressure (ABP) and transcranial doppler cerebral blood flow velocity from [13]. Model parameters \( (L, R_0, q_0, k) \) were selected to minimize mean quadratic deviation of modeled and measured rCBFV.

For simulation we used experimentally measured ABP data from Hwang PhD Thesis (2012). Besides in Fig. 3 the shape of CBFV is depended of ABP [13].

Effect of adding \( R_1 \), \( R_2 \) and \( R_3 \) on CBFV: Resistors in series (\( R_2 \) and \( R_3 \), 3-WM) decrease CBF pulse amplitude, while resistor \( R_2 \) in parallel with inductance (\( L \)) decreases effect of inductance and increases CBF pulse amplitude (Fig. 4), shape of CBF is unchanged.
Fig. 5. Change of CBFV depending on compartmental pressure.

Simulation of step increase in compartmental pressure E. As compartment pressure increases to mean arterial pressure (Fig 5, a), CBF ceases with preservation of low during systole and appearance of small amplitude back and forth oscillations (Fig. 5, b).

5 Conclusions

The research showed that modification of Windkessel model, with variable Starling resistor and nonlinear capacitor could be used to simulate dynamic blood flow, blood volume and resistance fluctuations in the collapsible vessel model. Model parameters and state equations have to be fitted with experimental data and fluid dynamics models to determine adequacy of approximation.

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7 References


