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Actively Circulating Volume as a Consequence of Stochasticity within Microcirculation

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Abstract

It is well established that in the pathology of the cardio-vascular system (CVS) only a portion of the blood volume (BV) can be in active circulation. This portion of BV is named the actively circulating volume (ACV) and is evaluated from a monotone decrease of dilution curve produced by an intravascular tracer. In given paper is presented Markov chain as a math model of the flow of a tracer throughout CVS. The consideration of CVS as a set of segments with respect to an anatomical structure and assuming the existence for CVS steady-state condition; leads to the Markov chain of the finite order with constant coefficients. The conclusions of the article are 1) there are open and closed microvessels, such that the switching from open to closed and back is a stochastic process, 2) if the switching is slow then the ACV, as the volume of heart chambers and only open for circulation vessels, can be detected.

Keywords: Blood Volume, Actively Circulating Volume, Microcirculation, Vasomotion, Markov Chain, Math Model of Cardiovascular System

1. Introduction

The importance of knowing BV is commonly accepted. However, BV is not routinely used in clinics or during experimental investigations. The primary drawback to measuring BV is that the mixing time for a tracer can vary from 2 - 3 min to 30 min [1]. Multiple blood-sampling method had been developed to solve the mixing dilemma. However, as stated by Wiggers [2], if mixing of a tracer requires more then 10 min, the resulting volume is not the volume responsible for cardiac output and the distribution of blood pressure. Thus, the concept that only part of the BV is actively circulating was developed [2], meaning that the BV separates into ACV and slow circulating volume (SCV). The analysis of blood sample data is based on a two-compartment representation of BV, such that within the ACV a tracer mixes instantaneously, and a slow exchange occurs between ACV and SCV [3,4]. The calculation of ACV is based on the back extrapolation of the indicator's concentration decay to the time of injection [4,5]. ACV could be up to 50% of BV [5,6]. In this paper we address the question: what could be a cause for the monotone drop of the concentration toward a steady state concentration (this concentration is used for BV calculation [1]). To answer this question we exploit the hypothesis made by Romanovsky in his monograph "Discrete Markov Chain" [6] that "the movement of blood particles in a human organism where the heart is the central point of branching, is a Markov (polycyclic) process."

A mathematical description of a tracer passing through the CVS began with the work of Stephenson [7]. He suggested that a dilution curve could be interpreted as a distribution of the time it takes for an indicator to pass through an organ. His approach was further developed by Meier & Zierler [8]. They established and generalized the relationship among mean transit time, flow, and blood volume based on the interpretation of dilution curves as a convolution of an input with a distribution of transit time. Application of operational methods, such as Laplace transform, to the distribution of time to pass different segments of the CVS leads to the system of linear equations for description of the evolution of a tracer throughout CVS [9]. If time is measured in car-diac-cycles and the CVS is a finite set of segments with respect to an anatomical structure then the flow of blood (and a tracer) can be described by a finite matrix A. The spectral decomposition of A leads to the conclusion: the concentration of an intravascular tracer in any systemic artery is described by the sum of three terms: 1) the steady-state

term corresponding to the complete mixing of a tracer; 2) the term of damped oscillations corresponding to the first pass and recirculation waves, and 3) the term of steadily (exponentially) decreasing items. An analysis of the conditions that enables the monotone decreasing term leads to the conclusion: the appearance of the SCV is due to the presence of closed microvessels and, additionally, the switching of the microvessels from the closed state to the open state and back is a slow process.

2. Mathematical Model for the Passage of an Intravascular Tracer

We begin with the assumption: the future trajectory of any blood particle depends only on the current site of the particle. A model based on the given assumption is a Markov chain [10] if it includes the following three components: 1) a structure of the CVS, 2) a distribution of a tracer throughout the CVS, and 3) an operator of the transition of the tracer throughout the CVS. In detail:

1) *A structure of the CVS.* It is a set of segments $\{S_k; k = 1 \cdots N\}$, such as the heart chambers, conductive vessels and microvessels. The segments are enumerated. The numeration starts with the right atrium (RA) designated as S_1. The numeration of other segments follows the rule that blood flows from the segments with lower subscripts to segments with the higher subscripts. Only the segments connected with the RA are exceptions to this rule. **Figure 1** demonstrated the numeration of segments beginning at the left ventricle.

2) *Distribution of a tracer throughout the CVS.* The distribution is a vector $\mathbf{z}(t) = \{z_k(t), k = 1, \cdots, N\}$, where the k^{th} component of $z(t)$ is the fraction of a tracer within the S_k at time t. As an initial distribution of a tracer, $z(0)$, will be taken $z_1(0) = 1$, and for all $k > 1$ $z_k(0) = 0$, meaning that a tracer is injected into the right atrium at time $t = 0$,

3) *An operator* $\boldsymbol{A} = \{a_{ij}\}$ that provides the transition of a tracer during one cardiac cycle, *where the* a_{ij} *is the fraction of a tracer within* S_i *that passes during one cardiac-cycle into* S_j: As a result the distribution of the tracer at time t, $\mathbf{z}(t)$, transforms to the distribution at time $t + 1$: $\mathbf{z}(t + 1) = \mathbf{z}(t)A$, and, recursively:

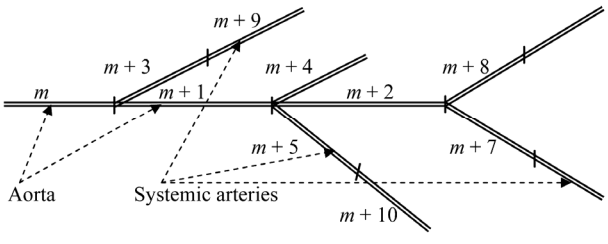

Figure 1. A possible numeration of the segments beginning with the left ventricle.

$$\mathbf{z}(t) = \mathbf{z}(0)\boldsymbol{A}^t \tag{1}$$

The text-book approach to dealing with (1) is to expand it through the characteristic numbers, $\{s_i\}$, (the roots of the equation $\mathrm{Det}(s\boldsymbol{A} - \boldsymbol{E}) = 0$). Thus the dilution curve recorded in the aorta, $z_m(t)$, is the power series of three components:

$$z_m(t) = b_{m1} + \sum b_{mi} s_i^{-t-1} + \sum \left|b_{mj}\right| \cdot \left|s_j\right|^{-t-1} \cos\left(\omega_j t\right) \tag{2}$$

where, b_{m1}, $\{b_{mi}\}$, $\{b_{mj}\}$, and $\{\omega_j\}$ are the combinations of eigenvectors of matrix $\boldsymbol{A}$ [10].

The examination of the components of (2) leads to the following:

1) The constant, b_{m1}, corresponds to the concentration of tracer after the mixing has been complited.

2) The second term, with all s_i real and > 1, is the steadily decreasing term; it will be connected with the detection of ACV.

3) The damped oscillating term, with the frequencies of oscillations $\{\omega_j\}$. All s_j are the complex numbers and, by modulus, > 1.

3. Results

The main conclusion of this article is the consequence of the statement: if diagonal elements of A, are zero $\{a_{ii} = 0\}$ then the equation $\mathrm{Det}(s\boldsymbol{A} - \boldsymbol{E}) = 0$ has only one real solution, $s_1 = 1$. The proof follows from the statement that two equations $\mathrm{Det}(s\boldsymbol{A} - \boldsymbol{E}) = 0$ and $F(s)=1$ are equivalent (see Appendix 1) ($F(s)$ is the generating function of the first pass throughout CVS). The equation for $F(s)$ is, see (A2):

$$F(s) = \sum p_k s^k = 1 \tag{3}$$

where p_k is the fraction of a tracer that passes through the CVS (from RA to RA) in k-cardiac-cycles. Since the p_k add to 1, then $s = 1$ is the only real positive characteristic number. Taylor decomposition of (3) at $s = 1$, leads to the other characteristic numbers. They are

$$s_k = 1 \pm 2\pi k i / F'(1); \quad k = 1, \cdots.$$

with $F'(1)$ as the mean transit time (MTT) for passage throughout CVS. Conclusion: thus, $z_m(t)$, see (2), has only damped oscillations around b_{m1} and the frequencies of damped oscillations are multiples of $2\pi / F'(1)$.

In other words, to have a steadily decreasing term in (2) we must have non-zero elements on the main diagonal of A. There are at least four $a_{ii} > 0$, and they correspond to the heart chambers. However, the mean time to pass any heart chamber is about 2 - 3 cardio-cycles (in pathological enlargement of the heart the time to pass can be up to 20 cm^3), thus the heart cannot be the cause of a monotone drop with the half-time 3 - 9 min. Consequently, there

must be non-heart elements $a_{ii} > 0$. The passage through such segments can be described as follows: if in the i-segment a tracer stays for a while, we should have at least two segments, let them be numbered $(i - 1)$ and $(i + 1)$, such that the tracer enters i-segment from $(i - 1)$ and leaves to $(i + 1)$-segment. Formally, from the $(i - 1)$-segment a tracer partly enters the i-segment and could partly enter the $(i + 1)$-segment, these parts are a_{i-1i} and a_{i-1i+1}, and will be denoted as β and $\alpha = 1 - \beta$. A tracer from i-segment partly stays for the next cardiac-cycle, and partly passes to the $(i + 1)$-segment, these parts are a_{ii} and a_{ii+1}, and are denoted as ν and $\mu = 1 - \nu$. The generating function to pass such construction is given by (4), see Appendix 2.

$$v(s) = \frac{\mu \cdot s}{1 - \nu \cdot s}\beta \cdot s + \alpha \cdot s; \quad (4)$$

There are two realizations of the formal construction, see **Figure 2**:

1) Required segment (with $a_{ii} > 0$) contains microvessels closed for circulation, and $(i - 1)$-segment contains perfused microvessels. When closed microvessel becomes open its content passes to $(i + 1)$ segment.

2) Segment (or a group of segments) is a mixing chamber, kind of "peripheral heart".

The following reasoning is based on the first realization. The first realization is chosen because 1) it is well established that practically in all tissues a part of microvessels is closed, and their recruitment is a way to respond to an increase in flow [11,12]; 2) in muscle tissue it is established that a fraction of ink-containing capillaries depends on the time of infusion of ink. For 4 sec of the infusion the fraction of ink-containing capillaries is about 12%, and for 90 sec infusion there are 90% of ink-containing capillaries [13]; 3) despite the presence of a kind of "peripheral" hearts, they fall far from the needed relation [volume]/[flow] be 3 - 9 min.

With non zero diagonal elements, the expression for a generating function for the passage of the CVS should include 1) the passage through the heart chambers with the generating function as $\prod_{j=1}^{4} \frac{b_j s}{1 - a_j s}$, where a_j and b_j are residual and ejection fractions of j-heart chamber; 2) the passage through the systemic and pulmonary conductive vessels; and 3) the passage through the microcirculation. The (5) gives the combined generating function, $F(s)$, to pass throughout CVS, where $F_1(s)$ includes the passage of the heart and conductive vessels, and the expression in the brackets is the generating function of the passage through microcirculation, $p_1 + p_2 = 1$.

$$F(s) = F_1(s) \cdot \left(p_1 F_3(s) + p_2 F_2\left(\alpha s + \beta s \frac{\mu s}{1 - \nu s} \right) \right) \quad (5)$$

Additionally to $F(s)$, given by (5), we introduce the generating function, $F_0(s)$, to pass CVS if there is no switching of the state (open/closed) of microvessels ($\beta = 0$ and $\alpha = 1$, **Figure 2**):

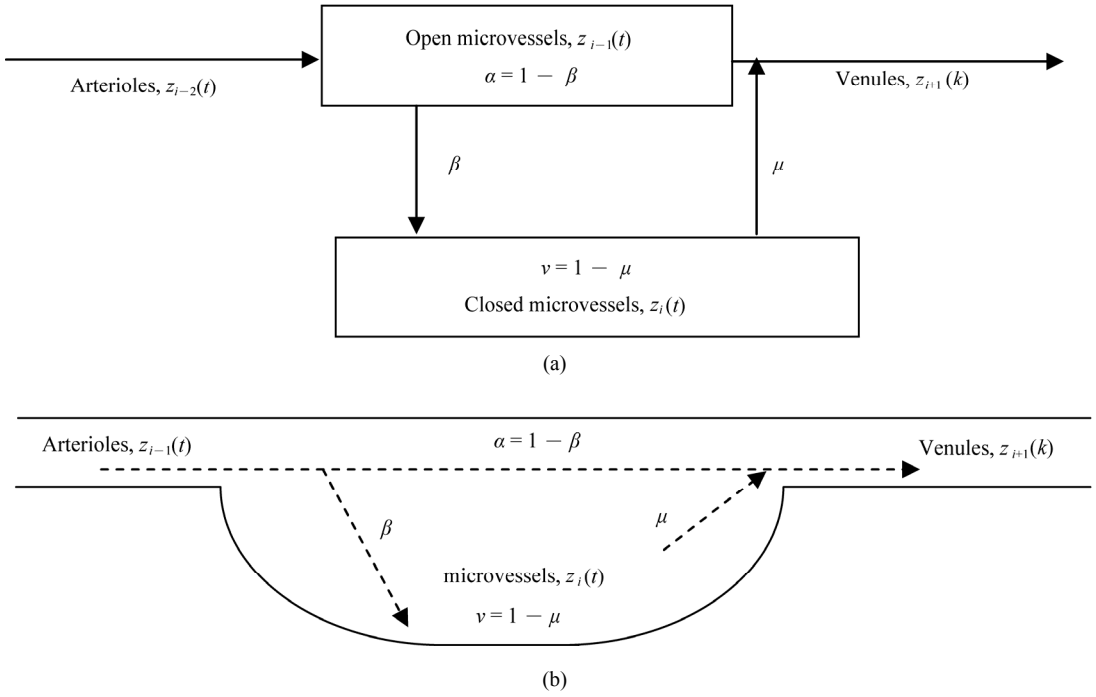

Figure 2. Two possible realizations for non-zero elements from main diagonal of A. (a) Schematic for stochastic exchange between open and closed microvessels; (b) Schematic for the passing of microvessels as a mixing chamber.

$$F_0(s) = F_1(s) \cdot \left(p_1 F_3(s) + p_2 F_2(s) \right) \quad (6)$$

Thus, our model of CVS has two distinct blood volumes:

1) Total blood volume, BV. By using established by Meier & Zierler [8] the relationship among mean transit time, flow, and volume we have:

$BV = F'(1) \cdot SV$, with SV as the stroke volume; (7)

2) A second blood volume, ACV, as the volume of open for circulation segments of CVS, such as heart chambers, conductive vessels, and open for flow microvessels. From (6):

$$ACV = F_o'(1) \cdot SV . \quad (8)$$

Now the aim of the article can be formulated as follows: the volume given by (8) and the volume obtained by back extrapolation, if monotone decrease of $z_m(t)$ exists are the same. In Appendix 3, there are derivations of the next parameters:

1) The expression for a concentration after complete mixing occurs, $b_{m1} = 1/F'(1)$.

$$z_m(\infty) = b_{m1} = \frac{1}{F'(1)} = \frac{SV}{BV}; \quad (9)$$

2) The expression for the real characteristic number, $s_2 > 1$,

$$s_2 = 1 + \frac{BV}{ACV}\mu \quad (10)$$

with ACV as the volume given by (8)

3) The term $b_{m2} = 1/F'(s_2)$ that is the factor at s_2, and the term $b_{m2} \cdot s^t = 1/F'(s_2) \cdot s^t$ is responsible for monotone decrease of $z_m(t)$. The back extrapolation of $z_m(t)$:

$$b_{m1} + b_{m2} = \frac{SV}{ACV} \Rightarrow ACV = \frac{SV}{b_{m1} + b_{m2}} \quad (11)$$

By compare (8) and (11) one can conclude that ACV as the volume of the heart, conductive vessels, and open microcirculation and ACV obtained by the back extrapolation of $z_m(t)$ are the same.

From (10) one has the condition to have a clear monotone decrease of the concentration of the intravascular tracer toward the steady state (and consequently to have opportunity to measure ACV): the μ should be small, such as $1/\mu \sim 3$ - 5 min (after cardiac cycles are transformed into minutes).

The volume SCV = BV – ACV with minutes constituting the mean time of returning to the circulation could be used as the explanation for the disorder: 1) the bends from the removal of N_2 since nitrogen in the tissue around microvessels constituent SCV has slow removal; 2) the urea rebound, since removing of the urea in patients under dialysis treatment from the tissue around of SCV is delayed [14]. Thus, the appearing of monotone decrease of $z_m(t)$ could be a the sign of microcirculation disorder.

There is a high probability that different parts of the microcirculation have different characteristics in the change of the state (open-closed) of microvessels. Consequently, (5) transforms into:

$$F(s) = F_1(s) \cdot \left(p_1 F_3(s) + \sum_{j=2}^{K} p_j F_j \left(\alpha_j s + \beta_j s \frac{\mu_j s}{1 - \nu_j s} \right) \right)$$
$$\text{with} \sum p_i = 1 \quad (12)$$

This poses the main problem with the traditional method for obtaining ACV. From Appendix 3 it follows that different μ in (12) lead to different real characteristic numbers, and the back extrapolation becomes dependent on the chosen time interval, the phenomena observed in the measurements of ACV [15].

4. Discussion

The main assumption, that leads to a Markov chain as a model for the transition of a trace throughout the CVS, is that every sequence of segments from the aorta to the right atrium and from the pulmonary trunk to the left atrium can be presented as a finite set. Two other assumptions are less significant. However, they simplify calculations: 1) the stability of hemodynamic, meaning that matrix A is a constant matrix, and 2) the velocity of blood is the same throughout the cross-section of any vessel.

Since the work of Krogh it has been well established that the recruitment of microvessels is the leading response of the tissue to the demand for nutrients [11,16]. Experiments with ink infusion [13] have demonstrated that the longer the infusion time the more microvessels are exposed to infused particles. Thus, the indirect evidence for the involvement of closed microvessels into the circulation under the steady-state conditions is established.

Back extrapolation of a tracer's decreased concentration is a way to obtain ACV [5,17]. The experiments and analysis presented in [15] point out the relatively low reliability of the back extrapolation, meaning that ACV depends on the time chosen for the back extrapolation. Consequently, it is plausible to suggest that different organs have different microcirculatory characteristics, thus a calculations based on a two-compartment presentation of CVS can produce low repeatability. The existence of microvessels that are out of circulation for more than 2 - 3 min should be considered when the rate and dosage of a drug is chosen.

5. Conclusion

ACV as the volume of heart chambers and only open for circulation vessels can be detected if the switching process is slow.

6. Competing Interests

The author declares that he has no competing interests.

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Appendix 1

The expression for the determinant of the matrix $\boldsymbol{B} = s\boldsymbol{A} - \boldsymbol{E}$, if all main diagonal elements of A are zeroes.

To obtain the Det$\boldsymbol{B}$ let take $b_{11}= -1$. By taking b_{11} we are forced to take only the elements from the main diagonal, thus the first term of DetB is $(-1)^N$. To get other terms of Det$\boldsymbol{B}$ let take the second non-zero element, sa_{12}, of the first row. The choice of next elements follows the repeatable procedure: 1) if the element sa_{ij} is chosen, the next element should be taken from j-row; 2) if in j-row there is the choice then the closest to the main diagonal element should be taken. The procedure continues unless we run into the element a_{k1}. The product of all chosen elements is $a_{12}a_{23}\cdots\cdots a_{k1}s^q$. This is the fraction of a trace that passes CVS by the chosen path for the time in q-cardiac-cycles. The product becomes the term of DetB after multiplication by $(-1)^{q+1}$, and by all b_{jj} where j are the numbers of the segments not presented in the given path. Since all $b_{jj} = -1$, we have the term of DetB as:

$$(-1)^{q+1} a_{12}a_{23}\cdots\cdots a_{k1}s^q (-1)^{N-q} \tag{A1}$$

The (A1) establishes the one-to-one correspondence between the paths throughout CVS and nonzero elements of Det$\boldsymbol{B}$, The sums of all terms of (A1) with the same time to pass CVS, let it be q, is the fraction of injected tracer such that passes CVS in q cardiac-cycles. Let denote this fraction as p_q. With the use of $\{p_q\}$ the equation, Det$\boldsymbol{B} = 0$ can be written as:

$$\sum_{q=1}^{M} p_q s^q = 1 \tag{A2}$$

with the M as the longest path from RA to RA.. By the definition [10] the left part of (A2) is the generating function for the first time to pass through the CVS, and will be denoted as $F(s)$.

Appendix 2

The equations for the evolution of the part of the $z(t) = (\cdots, z_{i-1}(t), z_i(t), z_{i+1}(t), \cdots)$, where subscript i denotes the non-heart segment of CVS with $a_{ii} > 0$, accordingly to **Figure 1** is:

$$\begin{aligned} z_i(t+1) &= \beta \cdot z_{i-1}(t) + \nu \cdot z_i(t) \\ z_{i+1}(t+1) &= \alpha \cdot z_{i-1}(t) + \mu \cdot z_i(t) \end{aligned} \tag{A3}$$

Multiplying both parts of (A3) by s^{t+1} and summing with respect to t, gives the following equation for connection between $z_{i-1}(t)$, and $z_{i+1}(t)$ in terms of a generating function:

$$Z_{i+1}(s) = \sum_t z_{i+1}(t)\cdot s^t = \left(\frac{\mu \cdot s}{1-\nu \cdot s}\beta \cdot s + \alpha \cdot s\right)\cdot Z_{i-1}(s) \tag{A4}$$

where $v(s) = \dfrac{\mu \cdot s}{1-\nu \cdot s}\beta \cdot s + \alpha \cdot s$ is the generating function for the passage through the segments $(i-1)$, (i), and $(i+1)$.

Appendix 3

The search for real characteristic numbers that are > 1.0.

The equation $v(s) = 1$ has two solutions $s_{v1} = 1$ and $s_{v2} = 1/(1-\beta-\mu)$. Between s_1 and s_2 there is the pole $s_p = 1/(1-\mu)$ of $v(s)$ and, consequently, of $F(s)$. Since in the interval (s_p, s_{v2}) the $F(s)$ varies from minus infinity to $F(s_{v2}) > 1$, $F(s) = 1$ has the solution in the given interval. The use of Taylor decomposition of $F_1(s)$, $F_2(s)$, and the difference for $v(s)$ in the vicinity of s_{v2} (the difference, not the derivative, is taken because of the proximity of the pole of $v(s)$) leads to the expression for the real characteristic number >1:

$$s_2 = 1 + \frac{F_1'(1) + p_1F_3'(1) + p_2F_2'(1)\cdot\dfrac{\mu+\beta}{\mu}}{F_1'(1) + p_1F_3'(1) + p_2F_2'(1)}\mu = 1 + \frac{BV}{ACV}\mu \tag{A5}$$

The coefficient at s_2, in the spectral decomposition of the $\boldsymbol{A}$, b_{m2}, is $1/F'(s_2)$ thus

$$b_{m2} = \frac{1}{F_1'(1) + p_1F_3'(1) + p_2F_2'(1)\cdot\left(1 + \dfrac{\mu}{\beta}\dfrac{\left(F_1'(1) + p_1F_3'(1) + p_2F_2'(1)\right)^2}{\left(p_2F_2'(1)\right)^2}\right)} \tag{A6}$$

The sum $b_{1m} + b_{m2}$, with b_{1m} given by $b_{m1} = \dfrac{1}{F_1'(1) + p_1F_3'(1) + p_2F_2'(1)\cdot\dfrac{\mu+\beta}{\mu}}$, is as follows:

$$b_{m1} + b_{m2} = \frac{1}{F'(1)} + \frac{1}{F'(s_2)} = \frac{1}{F_1'(1) + p_1F_3'(1) + p_2F_2'(1)} = \frac{SV}{ACV} \tag{A7}$$

