Shape of a dilution curve as the consequence of stochasticity within microcirculation.

Victor V. Kislukhin

viktork08@gmail.com

Abstract.

Introduction. There is a problem with commonly accepted parameters for microcirculation. This problem is due to many used mathematical models. The aim of notes to reveal that hypothesis about stochasticity of microflow leads to the uniqueness of mathematical equations for passage throughout microcirculation. Thus stochasticity could be a motivation for the choice of parameters of microcirculation.

Method. The passage throughout microcirculation is formed by next five events: (1) be in intravascular space, (2) be in extravascular space, (3) a microvessel is closed, (4) a microvessel is open, and also (5) a particle, being in open microvessel, experiences a variation of velocity.

Result: Markovian property leads to a uniqueness of distributions of named events and (a) the first four events are exponentially distributed; (b) the distribution of time to pass through open microvessels is infinitely divisible and is a gamma distribution.

Keywords: Stochasticity, Microcirculation, Poisson distribution, Gamma distribution, Indicator dilution, Diffusion.

1 Introduction.

For central hemodynamic there are such parameters as cardio-output, central blood volume, heart/ventricular volume. The same time parameters for microcirculation are numerous. This is due to the many used math models. For example, math models based on Krogh's model of oxygen exchange [1] ignore time and space heterogeneity of tissue perfusion [2], or calculations of endothelium permeability depend on assumption (thus math model) of low/high permeability of used indicator [3]. In models used stochastic description [4,5,6] is shown that the rate of vasomotion influences consumption of O2, or permeability of endothelium can be estimated by the use of Goresky transform [7]. Thus we have a problem with parameters of microcirculation based on what should be a choice of math model.

The main feature of microcirculation is its very irregular character of flow. Under a microscope can be seen that velocities of red blood cells are variable, including complete interruptions of the flow. Variation of flow is partly due to vasomotion [8], and

also due to: “The variations in the properties of blood cells, random temporal fluctuations of pressure, property of vessels wall” [9]. Thus it is plausible to assume stochasticity of irregularities.

Aim of notes is to reveal: If we accept stochasticity in form of stationary Markov process [10] then the events that constitute the passage of any indicators have unique math equations.

Thus we will have motivation for acceptance Goresky transform [11] as the tool for calculation permeability and the rate of vasomotion as criterion for state of microcirculation.

2 Mathematical model of stochasticity within microcirculation.

Next five events constitute the pass through microcirculation: (1) be in intravascular space, (2) be in extravascular space (for diffusible particles), (3) a microvessel is closed, (4) a microvessel is open, and (5) a particle, being in open microvessel, experiences a variation of velocity.

2.1 Notations for time.

For not specific time will be used t. There are also three specific times: (1) an r is a time to pass through a microcirculation by diffusible particles; (2) an s is the transit time for intravascular particles; (3) T is the time that intravascular particles spent in open microvessels, thus leaving time s-T as a time to be in closed microvessels.

2.2 Assumptions

1. The passage of particles is a stationary markovian (process where past influence future through present) process. 2. Diffusing particles pass through intravascular space as intravascular particles do thus following the distribution of s.
Consequently, r-s is the time that diffusing particles spend in extravascular space.

2.3 Math equations for first four events.

Assumed markovian property leads to exponential distributions for all four first events [10].

List of distributions with characteristic parameters is as follow:

1. Density of distribution to be in intravascular space is

$$f_\delta(t) = \delta \cdot \exp(-\delta t) \quad (1)$$

with 1/δ as the mean time to be in vascular space before entering tissue.

2. Density of distribution to be in extravascular space is

$$f_\gamma(t) = \gamma \cdot \exp(-\gamma t) \tag{2}$$

with 1/γ as the mean time for a particle to be in the tissue before returning into blood.

3. The time for resuming of flow has the density

$$f_\mu(t) = \mu \cdot \exp(-\mu t) \tag{3}$$

and 1/μ is the mean time for a resuming of flow.

4. The time for microvessels to be open has the density

$$f_\beta(t) = \beta \cdot \exp(-\beta t) \tag{4}$$

where 1/β is the mean time for a microvessel being open.

2.4 The 5th event. The passage through open microvessels or a distribution for T.

It will be shown that distribution of T, G(T), has as a density of a gamma distribution (5). The search for G(T) is based on the statement: G(T) is infinitely divisible [10]. To show this we follow to the next reasoning. In microcirculation due to the absence of inertia pressure gradient and velocity are instantly connected $V = k \cdot gradP$ [9]. Thus variations of pressure produce new velocities and also the variations of time to pass microcirculation. Now, if we divided each path within microcirculation on two about equal parts then the G(T) would become the convolution of two mutually independent distributions. Let denote them as $G_{1/2}$(T). We can continue this procedure thus G(T) can be presented as convolution of any number of distributions. Thus G(T) is infinitely divisible distribution.

Laplace transform of any distribution, particularly G(T) is $g(\lambda) = \int_0^\infty \exp(-\lambda T)\, G\{dT\}$, and for infinitely divisible $g(\lambda) = \exp(-\chi(\lambda))$,with $\chi(\lambda) = \nu \int_0^\infty \frac{1-\exp(-\lambda T)}{T} P\{dT\}$ and P(T) as probability distribution [10].

Since there is sequence $\lambda \to \infty$ such that $\frac{g(\lambda\tau)}{g(\lambda)} \to \tau^{-\nu}$ and with $\tau t = 1$, $\frac{G(Tt)}{G(T)} \to \frac{t^\nu}{\Gamma(p+1)}$ $T \to 0$, we can accept that g(λ) has regular variation [10]. Then to fulfill these conditions P(T) should be of the form: 1-exp(-aT). Thus G(T) has density:

$$f_{a,\nu}(T) = a^\nu \mathrm{T}^{\nu-1} \cdot \frac{\exp(-at)}{\Gamma(\nu)} \tag{5}$$

3 Equations of math model.

Equations 1 through 5 are the "bricks" from which a model of the passage of diffusible or intravascular indicators is made. We start with the search for D(r,s), the conditional (s is fixed) density of distribution to pass microcirculation by diffusible indica-

tor. The need of randomization of D(r,s) by distribution of s, V(s), $D(r) = \int D(r,s)V(s)ds$, lead us to the search for distribution to pass microcirculation by intravascular indicator. The search for V(s) is in two step: (a) obtaining conditional density of distribution, V(s,T), T=const, and (b) randomization of V(s,T) by distribution of T. Thus we have D(r) and V(s).

3.1 The passage of a diffusing indicator.

Since time between two jumps out of vascular space has density of exponential distribution, equation (1), the n jumps during time s has a Poisson distribution $p_n = \frac{\exp(-\delta s)}{n!}(\delta s)^n$ [10]. If a particle is not a consumable then appearance in tissue follows by returning into vasculature. Thus D(r,s) (with $f_\gamma^{0*}(r-s) = 1$ if r=s and zero if r>s) is:

$$D(r,s) = \text{e p}(-\delta s) f_\gamma^{0*}(r-s) + \text{e p}(-\delta s) \sum_{n=1}^{\infty} \frac{(\delta s)^n}{n!} f_\gamma^{n*}(r-s) \tag{6}$$

Laplace transform of (6) with $\varphi(\lambda) = \lambda \frac{\gamma+\delta+\lambda}{\gamma+\lambda}$ is:

$$d(\lambda,s) = \int \exp(-\lambda r)\, D(r,s)\, dr = \text{e p}\left(-s\lambda \frac{\gamma+\delta+\lambda}{\gamma+\lambda}\right) = \text{e p}(-s\varphi(\lambda)) \tag{7}$$

The (7) is a conditional Laplace transform. Now we need perform randomization of s in d(λ,s). The randomization of the expression (7) by distribution of s leads to the Laplace transform of the V(s) with the replacement of λ in $\exp(-\lambda s)$ by φ(λ):

$$d(\lambda,s) = \int \exp(-s\varphi(\lambda))\, V(s)\, ds \tag{8}$$

Thus our next step is to find the distribution for the s, V(s).

3.2 An intravascular indicator. The search for V(s,T).

The passage of an intravascular indicator is the composition of two processes (a) the change of the state of any microvessel, meaning that some closed microvessels become open and vice versa, and (b) a variation of the time T to pass through open microvessels. We start with T fixed.

Since time between two stops follows exponential distribution the probability of n stops is given by Poisson distribution, $p_n = \frac{\exp(-\beta T)}{n!}(\beta T)^n$. Every stop follows by resuming of flow. Thus we get a compound Poisson distribution for the transit time of an intravascular indicator with the density V(s,T), and $f_\mu^{0*}(s-T) = 1$ if s=T and 0, if s>T.

$$V(s,T) = \text{e p}(-\beta\text{T}) f_\mu^{0*}(s-T) + \text{e p}(-\beta\text{T}) \sum_{n=1}^{\infty} \frac{(\beta\text{T})^n}{n!} f_\mu^{n*}(s-T) \tag{9}$$

Laplace transform of (9) with $\phi(\lambda) = \lambda\frac{\beta+\mu+\lambda}{\mu+\lambda}$ is:

$$v(\lambda,T) = \int \exp(-\lambda s)\, V(s,T)\, ds = \text{e p}\left(-\lambda T\frac{\mu+\beta+\lambda}{\mu+\lambda}\right) = \text{e p}(-T\phi(\lambda)) \tag{10}$$

Thus we have conditional Laplace transform for intravascular indicator. Now final step: to obtain unconditional distributions for diffusing and intravascular indicators.

3.3 Unconditional distributions to pass through microcirculation.

The randomization of T in v(λ,T), equation (10), leads to Laplace transform for $f_{a,v}(T)$, only parameter λ is replaced by ϕ(λ):

$$v(\lambda) = \int \text{e p}[-T\phi(\lambda)]f_{a,v}(T)dT = a^v(a+\phi(\lambda))^{-v} \tag{11}$$

The unconditional Laplace transform for d(λ) is obtained in two steps: (a) from d(λ,s) as conditional Laplace transform, is obtained d(λ,T), with fixed T:

$$d(\lambda,T) = \int \exp\big(-s\varphi(\lambda)\big)\, V(s,T)\, ds = \text{e p}(-T\phi(\varphi(\lambda))) \tag{12}$$

(b) From d(λ,T), by randomizing T with $f_{a,v}(T)$ is obtained d(λ):

$$d(\lambda) = \int \text{e p}[-T\phi(\varphi(\lambda))]f_{a,v}(T)dT = a^v(a+\phi(\varphi(\lambda)))^{-v} \tag{13}$$

It is possible to transform expressions (11) and (13) into corresponding distribution functions. However for all practical purposes is better to analyze Laplace transformation itself.

3.4 Laplace Transform as the tool for investigations.

For example let consider consumption/sequestration. Now λ is the denotation for intensity of consumption. DP(λ) is a fraction of consumed indicator that passes through microcirculation. Since consumption takes place in the extravascular space, the time for consuming is r-s. If we assume that consumption follows to the first order differential equation, meaning that during time interval dr the fraction of consumed substance is λ [1] then:

$$\frac{dP(r)}{dr} = -\lambda P(r);\;\; P(r-s) = \exp(-\lambda(r-s)) \tag{14}$$

where P(r-s) is the fraction of the substance still in the tissue and not consumed or sequestrated.

Now we should take the distribution of (r-s) given by (6) and, after multiplication by (14), we get the conditional fraction of consumed indicator (the condition is fixed s):

$$DP(\lambda,s) = \int \exp(-\lambda(r-s))\, D(r,s)\, dr = \text{e p}\left(-s\lambda\frac{\delta}{\gamma+\lambda}\right) \tag{15}$$

The randomization of s in (15), with $f(\lambda) = \lambda \frac{\delta}{\gamma+\lambda}$ by V(s,T) leads to:

$$DP(\lambda, T) = \int \exp(-\mathrm{sf}(\lambda))\, V(s, \mathrm{T})\, ds = \mathrm{e\ p}\left(-\mathrm{Tf}(\lambda) \frac{\mu+\beta+f(\lambda)}{\mu+f(\lambda)}\right) \quad (16)$$

As the final step, we should randomize DP(λ,T) by the distribution of T, see (5):

$$DP(\lambda) = a^{\nu} \left(\mathrm{a} + \mathrm{f}(\lambda) \frac{\mu+\beta+f(\lambda)}{\mu+f(\lambda)}\right)^{-\nu} \quad (17)$$

4 Discussion.

There are many math models for blood flow throughout microcirculation. Particularly in use there are stochastic models. The comprehensive descriptions of stochastic models are given in [12, 13]. Application of stochastic approaches is based on the approximation of real dilution curves, meaning that parameters of chosen distributions become parameters of recorded curves. Such formal approach has problem with physiological interpretation of model's parameters.

In given manuscript, and this is its novelty, is shown that assumption of stochasticity leads to the uniqueness of math equations of model for blood flow.

Since four basic events: (1) to be in extravascular space, (2) to be in intravascular space, (3) a microvessel is closed, and (4) a microvessel is open, due to markovian property, follow to exponential distributions, we have a very effective application of Laplace transform. The combinations of these processes become compound Poisson distributions thus the combinations have Laplace transform as $exp(-t \cdot f(\lambda))$. The randomization of t in $exp(-t \cdot f(\lambda))$ by any distribution becomes Laplace transform of this distribution also, only λ is replaced by $f(\lambda)$.

5 Conclusion.

From the assumption of stochasticity follows uniqueness of distributions that formed the passage of indicator through microcirculation. Thus exponential distributions and their generalization, gamma-distribution, become the motivations for introducing the permeability of endothelium and rate of vasomotion as characteristics of microcirculation.

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