A Gibbs point field model for the spatial pattern of coronary capillaries

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Abstract

We propose a Gibbs point field model for the pattern of coronary capillaries in transverse histologic sections from human hearts, based on the physiology of oxygen supply from capillaries to tissue. To specify the potential energy function of the Gibbs point field, we draw on an analogy between the equation of steady-state oxygen diffusion from an array of parallel capillaries to the surrounding tissue and Poisson’s equation for the electrostatic potential of a two-dimensional distribution of identical point charges. The influence of factors other than diffusion is treated as a thermal disturbance. On this basis, we arrive at the well-known two-dimensional one-component plasma, a system of identical point charges exhibiting a weak (logarithmic) repulsive interaction that is completely characterized by a single dimensionless parameter. By variation of this parameter, the model is able to reproduce many characteristics of real capillary patterns.

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1. Introduction

Capillaries play a critical role in the transport of oxygen and nutrients to the myocardium and in the removal of metabolic waste products from the tissue [1]. In particular, the spatial pattern of coronary capillaries is an important factor in maintaining the balance between myocardial oxygen demand and supply. There has been considerable interest in a detailed morphometric description of the capillary network [2] as well as in modeling efforts directed toward a better understanding of oxygen supply to myocardial tissue [3–5]; for reviews see Refs. [6,7]. The appearance of capillary patterns may change substantially due to remodeling of myocytes and the extracellular matrix in patients with end-stage heart failure, most frequently caused by dilated cardiomyopathy (DCM), ischemic cardiomyopathy (ICM), or inflammatory cardiomyopathy (InfCM) [8]. Also, differential diagnosis of cardiomyopathies is still difficult and time-consuming [9,10]. Therefore, a model that characterizes the pattern of myocardial capillaries might serve as an input to calculations for the
assessment of oxygen supply to the myocardium and to simulation studies of other transport phenomena in the microcirculation of human hearts as well as an additional aid in the histopathologic diagnosis of various forms of heart failure.

Here, we propose a point field model for the spatial pattern of coronary capillaries and apply this model to characterize the capillary patterns we observed in transverse histologic sections from healthy hearts and from patients with end-stage heart failure due to DCM, ICM, or InfCM. Point fields (or, in mathematical terminology, point processes) have frequently been used to model spatial point patterns in such diverse fields of science as astronomy (locations of galaxies in space), geology (ore reserves), biology (locations of trees in a forest), and medicine (cell nuclei in histologic tissue sections); for review see, e.g., Refs. [11–14]. A spatial point process is any stochastic mechanism which generates a countable set of points in the plane [11]. The simplest—though the most important—point process is the homogeneous (“stationary”) planar Poisson process; it is the model for a completely random arrangement of points in the plane without any interaction (“complete spatial randomness”, CSR). As such, it serves as a reference (null hypothesis) for “tests of randomness” of a given spatial point pattern [15]. On the other hand, if there is some kind of interaction between the points, the resulting pattern either appears as more regular (repulsive interaction) or more clustered (attractive interaction) than CSR. In a recent study [16], we showed that the pattern of coronary capillaries in histologic sections from human hearts is more regular than CSR and regularity decreases in patients with end-stage heart failure caused by DCM, ICM, or InfCM. Since Gibbs point fields are good models for patterns with some degree of regularity [13], we have chosen this class of point field models to describe capillary patterns. In particular, we draw on an analogy between the equation of steady-state oxygen diffusion in tissue and Poisson’s equation for the electrostatic potential of a charge distribution and arrive at the two-dimensional one-component plasma (2D-OCP), a well-known model in statistical mechanics [17–19]. We use this system as the basis of a Gibbs point field and show that this stochastic model is able to reproduce many characteristics of real capillary patterns.

2. Methods

2.1. Histomorphometry

Tissue preparation and technical procedures of data acquisition and analysis have been described in detail elsewhere [16]. Briefly, transmural histologic sections from the left ventricular free wall were immunohistochemically stained with mouse monoclonal antibody (clone JC 70A, Dako, Glostrup, Denmark) directed against the endothelial cell marker protein CD31. In each histologic section, square pictures of side length 315 μm were taken at randomly selected locations in the subepicardial, midventricular, and subendocardial region by means of a light microscope (Orthoplan, Leitz Germany; magnification ×250) with an attached digital camera (Coolpix 5000, Nikon, Japan). The selected microscopic fields contained transversally oriented myocytes and were free of larger vessels and scar regions. Capillary profiles were identified on the basis of CD31-positive staining, morphology and a diameter of less than 10 μm. The centers of the capillary profiles were marked and the Cartesian coordinates of the marks were automatically retrieved by means of a program we developed with the MATLAB Image Analysis Toolbox (Mathworks, Natick, MA, USA).

The spatial pattern of capillaries was described by the distribution of metric and topologic properties of Voronoi polygons associated with the centers of capillary profiles, by the distribution of nearest-neighbor distances \( d \), as well as by means of the pair correlation function \( g(r) \). A Voronoi (or Dirichlet) polygon associated with a given point from a set of points in the plane consists of the region closer to this point than to any other point (for review, see Ref. [20]). The set of all Voronoi polygons completely tiles the plane and is referred to as a Voronoi tessellation. In particular, the statistics of polygon areas provides information about the spatial pattern of the underlying set of points [21]. Voronoi tessellations were calculated by means of the Qhull software package [22]. Qhull provides the vertex coordinates of the polygon-edges for all pairs of adjacent input points as well as the number \( N_e \) of edges for each polygon. From these data we calculated polygon areas \( A \), polygon perimeters \( S \), and nearest-neighbor distances \( d \). In addition, we considered an asphericity parameter \( z \) for Voronoi polygons, \( z = S^2/(4\pi A) \), which measures the deviation of the shape of a polygon from that of a circle. By definition, \( z = 1 \) for a circle and values \( z > 1 \) indicate more prolate polygons.
The pair correlation function $g(r)$ of a set of points measures the probability of finding another point at a distance $r$ from any given reference point of the set, normalized such that $g(r) \equiv 1$ for a purely random arrangement of points with the same numerical density. Thus, $g(r)$ describes the averaged local density around any given point of the distribution and characterizes the extent to which a given set of points deviates from CSR [23]. To estimate $g(r)$, we constructed a normalized frequency histogram of the separations of all point pairs for which at least one member had a minimum distance $r$ from the boundary [14,24].

2.2. Gibbs point field models

Originally, Gibbs processes were studied in the field of statistical mechanics of many-particle systems. There, the joint probability density $f(x_1, \ldots, x_N)$ of the positions $x_1, \ldots, x_N$ of a fixed number of $N$ particles in a finite region $V$ of space (i.e., of a pattern of points at $x_1, \ldots, x_N$) in thermal equilibrium at temperature $T$ (canonical ensemble) is given by the Gibbs canonical distribution (see, e.g., Ref. [23])

$$f(x_1, \ldots, x_N) = \frac{1}{Z_N(V, \beta)} \exp\{-\beta U(x_1, \ldots, x_N)\},$$  \hspace{1cm} (1)$$

where $U(x_1, \ldots, x_N)$ is the total potential energy of the particle configuration and the parameter $\beta = (k_B T)^{-1}$ is the inverse temperature of the system in energy units ($k_B$ is Boltzmann’s constant). The normalizing constant $Z_N(V, \beta)$ is the configurational part of the classical canonical partition function of $N$ interacting particles (“configuration integral”),

$$Z_N(V, \beta) = \int_{V^N} \exp\{-\beta U(x_1, \ldots, x_N)\} \, dx_1 \cdots dx_N.$$  \hspace{1cm} (2)$$

Frequently, $U$ can be written as a sum of pair potential energy functions $\phi(|x_i - x_j|)$, which describe the interaction between particles and which are assumed to depend only on the distance $r_{ij} = |x_i - x_j|$ between particle pairs:

$$U(x_1, \ldots, x_N) = \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \phi(r_{ij}).$$  \hspace{1cm} (3)$$

Many different functions $\phi$ have been studied in the literature as models for spatial point processes, including “hard core” models limiting particle separations to distances greater than a prescribed limit $\sigma$ (i.e., a system of hard spheres or discs of diameter $\sigma$) and “soft core” models resulting from weak repulsive forces (e.g., Ref. [25]).

Since capillaries supply the surrounding tissue with oxygen, it is unreasonable that they are positioned on a purely random basis: rather, each capillary should be found at the location where the oxygen concentration due to the presence of all other capillaries and oxygen sinks is a minimum. We may thus postulate some kind of “repulsion” between capillaries. To capture this “repulsive interaction” for use as a potential energy function in a Gibbs point field model, we draw on a formal analogy between the equation of steady-state oxygen diffusion in tissue and Poisson’s equation for the electrostatic potential of a given charge distribution.

2.3. An electrical analogue for oxygen diffusion from capillaries to tissue

As a model for the diffusion of oxygen (or any other substance) from capillaries to tissue we first consider a single capillary of infinite length, i.e., a line source with intensity $I$ per unit length. Neglecting axial diffusion and assuming steady-state conditions, diffusion in each plane perpendicular to the capillary is governed by Poisson’s equation [26,27]

$$D \Delta c(x) = -I \delta(x) + M,$$  \hspace{1cm} (4)$$

where $c(x)$ is the local oxygen concentration, $\Delta$ is the Laplace operator, $D$ is the oxygen diffusion coefficient, $M$ is the metabolic rate of oxygen consumption of the tissue, and $\delta(x)$ denotes the two-dimensional Dirac delta function. More generally, steady-state diffusion due to $N$ sources of equal intensity $I$ located at $x_j$ in a two-
dimensional domain $\Omega$ (corresponding to an array of parallel capillaries) can be described by

$$\Delta c(x) = -s \left[ \sum_{j=1}^{N} \delta(x - x_j) - m \right], \quad (5)$$

where $s = I/D$ and $m = M/I$. Boundary conditions compatible with steady-state diffusion are no-flux (Neumann-type) conditions, i.e., $\nabla c \cdot n = 0$, with $n$ being the outward-pointing normal vector to the boundary of $\Omega$.

On the other hand, the time-independent diffusion equation for substance concentration due to sources and sinks is analogous to Poisson’s equation for the electrostatic potential of a given charge distribution (cf. Ref. [28]). In particular, Eq. (5) is analogous to Poisson’s equation for the electrostatic potential $\varphi(x)$ of $N$ point charges $q$ in a finite two-dimensional domain $\Omega$ of area $A$ with a homogeneous neutralizing background and Neumann boundary conditions [29],

$$\Delta \varphi(x) = -2\pi q \left[ \sum_{j=1}^{N} \delta(x - x_j) - \frac{N}{A} \right], \quad (6)$$

where the term $-qN/A$ is the background charge density in $\Omega$. The system described by Eq. (6) is known as the 2D-OCP [18,19]; for review, see Hansen [30].

If we argue that each point charge (i.e., capillary) is located at the minimum of the potential $\varphi(x)$ (i.e., oxygen concentration $c(x)$) generated by all the other charges, also the total potential energy $U$ of such a configuration exhibits a minimum—ideally, identical point charges would organize themselves onto a regular lattice. However, regular lattice positions are not observed for real capillaries: thus, if we further hypothesize that the cumulative effect of the other determinants of capillary positions (such as vascular growth factors, the presence of myocytes and the extracellular matrix, pathological remodeling, a random environment per se) can be modeled by a Boltzmann distribution of $U$ with thermal noise due to a finite temperature $T$, we arrive—by way of analogy—at a Gibbs point field model, Eq. (1), with pair potential energy function $\phi$ of the 2D-OCP.

2.4. 2D-OCP

The 2D-OCP represents a system of $N$ identical point particles each carrying a charge $q$, imbedded in a neutralizing uniform background of opposite total charge and interacting via the logarithmic 2D Coulomb potential with potential energy function

$$\phi(r_{ij}) = -q^2 \log(r_{ij}/L), \quad (7)$$

where $L$ is an arbitrary scaling length. Since all particles carry the same charge, Eq. (7) describes repulsive forces between particle pairs.

A peculiarity of the OCP is the fact that it is composed of point particles, so that there is no characteristic length scale. Therefore, it is convenient to define a unit of length as the radius $a$ of a disk containing one particle on average (“ionic radius”), $a = (\pi \rho)^{-1/2}$, and to choose $L = a$. This unit of length will be used throughout the paper (i.e., reduced distances $r^* = r/a$ and the reduced number density is $\rho^* = 1/\pi$).

From Eqs. (1)–(7) it follows that an equilibrium state of the 2D-OCP is completely characterized by the single dimensionless coupling constant

$$\Gamma = \frac{q^2}{k_B T}. \quad (8)$$

$\Gamma$ is a measure of the Coulomb potential energy of the system over its kinetic thermal energy. Thus, $\Gamma$ represents the extent of thermal disturbance of the system due its temperature $T$. For $\Gamma = 2$, all equilibrium static properties of the 2D-OCP can be calculated exactly, providing a test for approximate theories and simulation results. For instance, the pair correlation function for $\Gamma = 2$ is given by $g(r^*) = 1 - \exp(-r^{*2})$ [17]. Moreover, Jancovici [17] obtained the following approximation of $g(r^*)$ from a temperature expansion of the
exact distribution functions in powers of \((\Gamma - 2)\) around \(\Gamma = 2\),
\[
g(x, \Gamma) = 1 - \exp(-x^2) + (\Gamma - 2)\{ -\exp(-x^2)[\log(x^2) + \gamma] \\
+ Ei(-x^2) - \frac{1}{2}Ei(-\frac{1}{2}x^2) + \frac{1}{2}\exp(-x^2)Ei(\frac{1}{2}x^2) \} + \ldots,
\]
where \(x = r^* = r/a = r\sqrt{\pi\rho}\) are reduced distances, \(\gamma = 0.5772\ldots\) is Euler’s constant, and \(Ei(x)\) is the exponential integral [31]
\[
Ei(x) = \int_{-\infty}^{x} \frac{e^t}{t} \, dt \quad (x > 0).
\]

2.5. Computer simulations

Simulations of the 2D-OCP were performed by the Metropolis Monte Carlo method [32] in the canonical ensemble with a fixed number of \(N = 192\) particles in a hexagonal box with periodic boundary conditions. Since the 2D-OCP crystallizes in a hexagonal lattice structure (at \(\Gamma \approx 140\)), a hexagonal simulation box compatible with this lattice structure was used (consequently, \(N = 3m^2, m\) integer). All simulations were started from a random arrangement of particles and equilibrated for \(10^5\) passes (attempted Monte Carlo moves per particle).

For a system with long-range Coulomb interactions, possible artifacts due to the finite size of the sample are minimized by letting each particle interact not only with all other particles in the simulation box but also with all particles of an infinite periodic array of replicas of the central box. When evaluated by the method of Ewald (e.g., Ref. [24]), the total potential energy of a system with logarithmic interactions such as the 2D-OCP is given by [19]
\[
U = \frac{q^2}{4} \sum_{\mathbf{n}} \sum_{ij} E_1[\eta^2(\mathbf{r}_{ij} + \mathbf{n})^2] + \frac{\pi}{A} \sum_{k \neq 0} \frac{\exp(-k^2/4\eta^2)}{k^2} \left| \sum_{j=1}^N q \exp(ik \cdot \mathbf{r}_j) \right|^2
- \frac{N^2\pi q^2}{4\eta^2A} - \frac{Nq^2}{4} (\gamma + \log(\eta^2a^2)).
\]

The first sum is over all lattice vectors \(\mathbf{n}\) of the hexagonal (real space) lattice and the second term is a sum over all vectors \(\mathbf{k} \neq 0\) of the reciprocal (Fourier space) lattice. The prime indicates that for \(\mathbf{n} = (0,0)\) the term \(i = j\) has to be excluded. \(A\) denotes the area of the hexagonal simulation box. \(\eta\) is an adjustable parameter that governs the rate of convergence of the two series in (11) and was set to \(\eta = 6.0/b\), where \(b\) is the side-length of the simulation box. With this value of \(\eta\), the cutoff in Fourier space can be set to \((k/k_{\text{min}})^2 \leq 200\) and the real space sum may be truncated after the \(\mathbf{n} = (0,0)\) term. Finally, \(E_1(z)\) denotes the exponential integral [31]
\[
E_1(z) = \int_z^{\infty} \frac{e^{-t}}{t} \, dt.
\]

The parameter \(\Gamma\) was varied from \(\Gamma = 0.1\) to 100. For each value of \(\Gamma\), 100 equally spaced equilibrium configurations from production runs comprising \(10^6\) passes were selected and saved to disk for later analysis.

2.6. Estimating \(\Gamma\) from experimental data

In order to compare simulation results with experimental data from histologic sections, these data were cast into the same dimensionless form as the 2D-OCP model: length \(r\) was converted into \(r^* = r(\pi\rho)^{1/2}\), where \(\rho\) is the respective capillary density of each individual microscopic field (see Section 2.4). Likewise, area \(A\) was expressed as \(A' = A\pi\rho\). Furthermore, simulated 2D-OCP configurations were transformed from the hexagonal simulation box into a rectangular box in order to be consistent with the analysis of the experimental data. For the same reason, Voronoi tessellations of the 2D-OCP model were performed without utilizing periodic boundary conditions (to eliminate edge effects, boundary polygons were excluded from the analysis). The coupling parameter \(\Gamma\) of the 2D-OCP model was estimated by comparing geometric and
topologic quantities of Voronoi polygons with corresponding experimental data from histologic sections. In the case of $\sigma_A, \langle z \rangle, \sigma_z, \sigma_{N_c}, \langle d^r \rangle$, and $\sigma_{d^r}$, the model parameter $\Gamma$ was estimated by simply reading it off the plots of the respective simulated quantities as functions of $\Gamma$ (see Section 3.3). In the case of $g(r)$, $\Gamma$ was estimated by fitting the approximate pair correlation function $g(r^*)$, Eq. (9), to the experimentally determined $g(r^*)$-values.

3. Results

3.1. Histomorphometry

Fig. 1 shows examples of microscopic fields in histologic sections from control and ICM hearts and the corresponding Voronoi tessellations resulting from the centers of the capillary profiles as generating points. These examples illustrate that capillary patterns appeared more “regular” in healthy hearts than in hearts from patients with end-stage heart failure. Table 1 summarizes the results we obtained from histomorphometry and Voronoi polygon analysis for the control, DCM, ICM, and InfCM group [16].

3.2. Characteristics of the 2D-OCP model

Fig. 2 displays equilibrium configurations of the 2D-OCP model together with associated Voronoi tessellations for four selected values from a wide range of the coupling parameter $\Gamma$, to illustrate the effect of $\Gamma$ on the pattern of the generated point fields: small values of $\Gamma$ (i.e., weak coupling/repulsion) produce relatively disordered states, whereas large values of $\Gamma$ (i.e., strong coupling/repulsion) entail more regular patterns. Figs. 3 and 4 show examples of how various characteristics of the simulated point patterns vary with the coupling parameter $\Gamma$. 

Fig. 1. Top: Photomicrographs showing examples of microscopic fields (side length 315 µm) from histologic sections of left ventricular myocardium with CD31-positive capillary profiles for patients in the control (left) and ICM group (right). Bottom: Voronoi tessellations of capillary centers corresponding to the photomicrographs displayed above; open circles indicate locations of capillaries associated with boundary polygons.
Fig. 5 shows two examples for geometric and topologic quantities of the 2D-OCP model as functions of the coupling parameter \( G \) in the range from \( G = 0.1 \) to 100. From these functions and the experimentally observed values of the respective quantities, the parameter \( G \) of the corresponding 2D-OCP model was directly read off by fitting (on a semi-logarithmic scale in the range from \( G = 1 \) to 10) a linear function to the data points of the model and determining the value of \( G \) that reproduced the intersection point of the horizontal line from the experimental value and the straight line from the fit. Fig. 6 shows the results of nonlinear least-squares fits of the approximate pair correlation function \( g(r^*) \) of the 2D-OCP model, Eq. (9), to experimentally observed \( g(r^*) \)-values for the control, DCM, ICM, and InfCM group. \( G \)-values thus estimated are summarized in Table 2.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>CD (No./mm²)</th>
<th>( A (\mu m^2) )</th>
<th>( x )</th>
<th>( N_e )</th>
<th>( d (\mu m) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1956 ± 231</td>
<td>512 ± 156</td>
<td>1.28 ± 0.11</td>
<td>5.93 ± 1.00</td>
<td>16.5 ± 4.3</td>
</tr>
<tr>
<td>DCM</td>
<td>1694 ± 292</td>
<td>599 ± 204</td>
<td>1.29 ± 0.11</td>
<td>5.93 ± 1.02</td>
<td>17.5 ± 5.0</td>
</tr>
<tr>
<td>ICM</td>
<td>1092 ± 181</td>
<td>919 ± 324</td>
<td>1.30 ± 0.12</td>
<td>5.90 ± 1.05</td>
<td>21.3 ± 6.6</td>
</tr>
<tr>
<td>InfCM</td>
<td>1142 ± 254</td>
<td>881 ± 369</td>
<td>1.30 ± 0.13</td>
<td>5.93 ± 1.08</td>
<td>20.4 ± 6.6</td>
</tr>
</tbody>
</table>

CD: capillary density; \( A \): area of inner Voronoi polygons; \( x \): asphericity parameter; \( N_e \): number of edges of inner Voronoi polygons; \( d \): nearest-neighbor distance.

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Fig. 2. Equilibrium configurations of the 2D-OCP model together with their Voronoi tessellations for selected values of the coupling parameter \( \Gamma \). Top: \( \Gamma = 0.2 \) (left), \( \Gamma = 2 \) (right). Bottom: \( \Gamma = 20 \) (left), \( \Gamma = 100 \) (right).
4. Discussion

Point field models have been used to characterize spatial point patterns in various fields of biology and medicine (e.g., Refs. [11,33]). However, to the best of our knowledge, such models have not been applied to describe the pattern of coronary capillaries. Here, we have borrowed the 2D-OCP model from statistical mechanics and have interpreted this well-known model as a Gibbs point field (in fact, we were led to the 2D-OCP by the shape of the pair correlation function we observed for capillaries, Fig. 6). The 2D-OCP is characterized by a weak (logarithmic) repulsion of its constituents, Eq. (7). Ogata and Tanemura [25] discussed a class of Gibbs point field models utilizing pair potentials that ranged from very-soft-core (VSC), soft-core (SC) to hard-core (HC) types of repulsive interactions. These authors modeled the patterns of Spanish towns by means of VSC potentials and reported pair correlation functions similar to the ones we observed for capillary patterns. Thus, their VSC models might also prove useful to describe the pattern of coronary capillaries. On the other hand, the 2D-OCP model is well established in statistical mechanics and is supported by the analogy between steady-state oxygen diffusion in tissue and the pair potential energy function of the Gibbs point field model. Moreover, there is an approximate expression for the pair correlation function \( g(r^*) \), valid around \( \Gamma = 2 \), Eq. (9). This allows to estimate \( \Gamma \) by a straightforward nonlinear least-
squares fit of Eq. (9) to experimental data (see Fig. 6). However, \( \Gamma \)-values extracted from experimental data by means of Eq. (9) systematically underestimate the true values: by applying Eq. (9) to simulated \( g(r^*) \)-data of known \( \Gamma \), we found for \( \Gamma \) in the range from 3 to 5 an error in the retrieved \( \Gamma \)-values ranging from 7% to 26%.

Values for the coupling parameter \( \Gamma \) as estimated from various experimental quantities (Table 2) were reasonably consistent with respect to \( \langle z \rangle \), \( \sigma_{z} \), \( \sigma_{N_e} \), \( \langle d' \rangle \), \( \sigma_{d'} \), and \( g(r^*) \): \( 4.19 \pm 0.78 \) (mean \pm SD) in the control group (range 3.07–4.96), \( 3.69 \pm 0.74 \) in the DCM group (range 2.61–4.54), \( 2.87 \pm 0.62 \) in the ICM group (range 1.72–3.55), and \( 2.47 \pm 0.56 \) in the InfCM group (range 1.60–3.16). The only exceptions were the \( \Gamma \)-values we obtained from the standard deviations of dimensionless polygon areas, \( \sigma_{A} \). These values were systematically smaller by a factor of about 4 (Table 2), thus underestimating the variability of polygon areas associated with capillary centers. This problem might be tackled by modifying the 2D-OCP model to include charges of varying magnitude instead of identical point charges; thereby, however, some benefits of the model, in particular, the fact that there is only one adjustable parameter, will be lost. On the other hand, Egginton [33] pointed out that the complex inhibitory interactions between neighboring capillaries are probably not accessible to straightforward analysis, e.g., due to the presence of myocyte fibers, any zone of inhibition around a capillary must be asymmetric, having both a radial and a circumferential component.

In the literature, spatial patterns have been characterized by first-order (described by the local density \( \rho(x) \)) as well as by second-order properties (describing the variation in the relative frequency of pairs of points as a
function of their position). Here, we have used the pair correlation function, $g(r)$, to describe the second-order behavior of point processes. However, $g(r)$ does not convey all the important information about a point process: quite different point processes may have the same $g(r)$ [13]. Therefore, we have employed an additional method to characterize point patterns, namely metric and topologic properties of Voronoi polygons [21]. Originally, Voronoi polygons were applied as capillary domains in the context of the Krogh model for oxygen supply to tissue [34] and to measure the heterogeneity of capillary spacing [2]. In subsequent studies, Voronoi polygons were used to describe spatial patterns, such as end-points of arteries in the chorioallantoic membrane of chicken eggs [35], or the spatial distribution of neurons in histologic sections of the human cerebral cortex [36]. Finally, we note that for the 2D-OCP model there are additional quantities that could be utilized to characterize the observed point patterns (e.g., fluctuations of the particle number in a given area, which should be proportional to the area perimeter [37]); in the present work, however, we have confined ourselves to quantities that can be reliably calculated, given our limited samples of experimental data.

Transport of oxygen from capillaries to tissue depends, among other determinants, on the arterial oxygen pressure, the blood flow through the capillaries, and on the intercapillary distance [38]. Table 1 shows an increasing variability of intercapillary distance $d$ from control to DCM, ICM, and InfCM; this trend is
reflected in the model parameter $G$ (Table 2). Turek and coworkers [38,39] introduced the concept of variability of intercapillary spacing as an independent determinant for tissue oxygenation: in the context of Krogh’s model [3], an increased variability of intercapillary distance proved to considerably impair tissue oxygenation.

Blood vessel formation is a complex process that involves a plethora of biochemical and mechanical factors [40]. Here, we have proposed a simple, mechanistic model for capillary patterns as observed in transverse histologic sections of myocardial tissue. Our approach is based on the assumption that capillary positions can be described by a Boltzmann distribution with certain parameters, Eq. (1). Such a distribution is characterized by the total potential energy $U$ and the temperature $T$ of the system under consideration. Based on the notion of a “repulsive interaction” between capillary centers due to their task of having to supply the surrounding tissue with oxygen, we have constructed $U$ from an analogy between the equation of steady-state diffusion in the presence of sources and sinks and Poisson’s equation for the electrostatic potential of a charge

\[
g(r^*) \equiv 1 \text{ for a random distribution of points in the plane is shown as a reference horizontal line.}
\]

\[
A^*: \text{dimensionless area of inner Voronoi polygons; } \alpha: \text{asphericity parameter; } N_e: \text{number of edges of inner Voronoi polygons; } d^*: \text{dimensionless nearest-neighbor distance; } g(r^*): \text{pair correlation function.}
\]

Table 2

<table>
<thead>
<tr>
<th></th>
<th>$\sigma_{A^*}$</th>
<th>$\langle \alpha \rangle$</th>
<th>$\sigma_\alpha$</th>
<th>$\sigma_{N_e}$</th>
<th>$\langle d^* \rangle$</th>
<th>$\sigma_{d^*}$</th>
<th>$g(r^*)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.11</td>
<td>4.71</td>
<td>4.22</td>
<td>4.77</td>
<td>4.96</td>
<td>3.07</td>
<td>3.40</td>
</tr>
<tr>
<td>DCM</td>
<td>1.01</td>
<td>3.73</td>
<td>4.03</td>
<td>4.19</td>
<td>4.54</td>
<td>2.61</td>
<td>3.01</td>
</tr>
<tr>
<td>ICM</td>
<td>0.73</td>
<td>2.99</td>
<td>2.97</td>
<td>3.21</td>
<td>3.55</td>
<td>1.72</td>
<td>2.76</td>
</tr>
<tr>
<td>InfCM</td>
<td>0.45</td>
<td>2.98</td>
<td>2.37</td>
<td>2.27</td>
<td>3.16</td>
<td>1.60</td>
<td>2.41</td>
</tr>
</tbody>
</table>

$\sigma_{A^*}$: dimensionless area of inner Voronoi polygons; $\langle \alpha \rangle$: asphericity parameter; $\sigma_\alpha$: number of edges of inner Voronoi polygons; $\sigma_{d^*}$: dimensionless nearest-neighbor distance; $g(r^*)$: pair correlation function.

Fig. 6. Experimental values of the pair correlation function $g(r^*)$ for the control, DCM, ICM, and InfCM group (open circles). Solid lines show nonlinear least-squares fits of the approximate pair correlation function of the 2D-OCP model as given in Eq. (9). The resulting best-fit values for the coupling parameter $\Gamma$ are displayed in the insets. The pair correlation function $g(r^*)$ is 1 for a random distribution of points in the plane is shown as a reference horizontal line.
distribution. The influence of factors other than diffusion is treated as a thermal disturbance and incorporated into the temperature parameter $T$. This application of a temperature parameter is similar to the approach reported by Zou and Wu [41] in their work on spatial patterns of interacting biological entities. A different treatment of capillary patterns was reported by Gamba et al. [42]; these authors used the diffusion equation and an analog of Burger’s equation to model the formation of capillary networks.

Finally, we note that our simulations of the 2D-OCP were performed in the canonical ensemble, i.e., using a fixed number of particles. On the other hand, the number of capillaries observed in the respective microscopic fields varied up to a factor of two between groups (see Table 1). In order to compare model predictions with experimental quantities, we expressed real number density $\rho$ in the same dimensionless form $\rho^*$ as in the 2D-OCP model. Although capillary density by itself is an important index to differentiate between healthy and failing hearts [43], we feel that our approach is justified, since we are primarily interested in patterns, i.e., in properties independent of scale. Further limitations of our model are that (i) it treats diffusion as a two-dimensional process; (ii) capillaries are considered as identical point (line) sources of oxygen; and (iii) it does not take into account the various levels of heterogeneities present in the microcirculation, e.g., adjacent cells with different oxygen consumption rates, capillaries with high and low blood flows [6].

In conclusion, we have shown that many properties of capillary patterns can be modeled by the 2D-OCP, a Gibbs point field exhibiting a weak repulsive interaction between its constituents and being completely characterized by their relative coupling strength $\Gamma$. Cardiac remodeling associated with DCM, ICM, and InfCM, entails capillary patterns less regular than the ones observed in healthy hearts and can be qualitatively described by a decreasing repulsion of capillary centers, i.e., by reducing the coupling parameter $\Gamma$ of the model from $\Gamma \approx 4.2$ (healthy hearts) to $\Gamma \approx 2.5$ (InfCM). In addition to a possible contribution of point field models to a better understanding of the processes involved in remodeling during DCM, ICM, and InfCM, these models might serve as a supplementary aid in the histopathologic diagnosis of various forms of heart failure as well as a basis for simulation studies of various transport phenomena in the microcirculation of the healthy and the failing heart.

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References
