Network emergence and reorganization in confined slime moulds

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Abstract
A fundamental question regarding biological transport networks is the interplay between the network development or reorganization and the flows it carries. We use Physarum polycephalum, a true slime mould with a transport network which adapts quickly to change of external conditions, as a biological model to make progress in this question. We explore the network formation and reorganization in samples suddenly confined in chambers with ring geometry. Using an image analysis method based on the structure tensor, we quantify the emergence and directionality of the network. We show that confinement induces a reorganization of the network with a typical 10^4 s timescale, during which veins align circumferentially along the ring. We show that this network evolution relies on local dynamics.

Supplementary material for this article is available online

1. Introduction

Biological transport networks are crucial for the functioning of many organisms. Examples include the vasculature of vertebrates (from aorta to capillary bed) and plants (from roots to leaf venation), the bronchial system, and the mycelium of fungal colonies. Such self-organized structures exhibit a number of properties that are highly desirable for technical applications: their efficiency in conveying fluid over long distances at reduced cost, their adaptability to changes in external conditions, and their resilience to damage are sources of inspiration for building artificial transport networks. The understanding of their formation and evolution has also obvious medical applications, as numerous diseases are associated with pathological evolutions of their structure. It is well documented that growth and remodeling of biological transport networks are influenced by mechanical factors [1, 2].

A challenging issue regarding biological transport networks is to understand the interplay between flow and network emergence and reshaping (coined respectively as vasculogenesis and angiogenesis for the vascular network of vertebrates). The slime mould Physarum polycephalum in its plasmodium stage, is a giant multinucleated single cell organism that develops a network of tubular elements in which flows are generated by contractions of the actomyosin cortex contained in the surrounding membrane [3, 4]. Even in the absence of a pacemaker like the heart, cortex dynamics can self-organize to give rise to coordinated flows on large scales [5–9]. In comparison, the interplay between this contractile activity, the flow they induce, and the network self-organizing dynamics has been poorly investigated: usually, network architecture is considered as static elements when studying contractile activity [10–12]. Actually, segmenting the network structure and tracking its evolution are heavy computational tasks.

In spite of its apparent simplicity, the development of this network shares common features with the development of vascular systems in higher organisms [13], or with the mechanisms that take place in the irrigation of tumours [14]. In particular, one can clearly identify two stages in the
development of the network: a growing phase during which
*P. polycephalum* develops a dense and reticulated network of
small tubular elements. Then a reorganizing phase during
which the network becomes more hierarchical and less
reticulated [15]. The self-organizing behavior of its tubular
network has shown to be useful to solve complex problem [16].
Its two-dimensional growth and rapid change in external
conditions make it a model organism to identify the mechanisms
involved in the formation and evolution of biological transport
networks.

In a previous study [8], we investigated the stable con-
tractile patterns emerging in a *Physarum plasmodium*
confined in an annular chamber. This geometry has numerous
advantages: it reduces the problem to a quasi-unidimensional
system while preserving the structural heterogeneities of a
(macro)plasmodium. Moreover, the periodic boundary con-
ditions suppress antero-posterior axis and so pre-established
polarity of the giant cell, while confinement prevent plas-
modium growth or displacement.

In the present paper, we investigate the emergence and
reshaping of the transport network for plasmodia confined in
annular geometries. For this purpose, rather than using computa-
tionally heavy network segmentation tools, we use a coarse-
grained description based on the structure tensor [17, 18].

2. Methods

The experimental set-up we use is the one described in [8]:
*Physarum polycephalum* sclerotia are obtained from Carolina
Biological, South Carolina, USA. Plasmodia are grown in
Petri dishes half filled with aqueous gel. Glucose is added to
the gel to prevent specimen exhaustion, but is kept at a suffi-
ciently low concentration to avoid bias caused by chemotaxis.
Two gel compositions are used to test the effect of nutrient
availability on network reshaping [19]: the first one is com-
posed of 2% Phytagel, 1% glucose, and 2% oatmeal agar, the
second one of 2% Phytagel and 1% glucose.

Petri dishes are sealed with parafilm and kept in a dark
chamber at 25 °C controlled temperature. Once or twice a
week, the growing front of a few plasmodia is cut off and
transferred to a fresh gel. The plasmodia are left to grow for
a typical period of 10–20 h. After they have homogeneously
recovered the gel, what is favored by the presence of glucose
[19], thin plastic rings are used to punch several concentric
annular plasmodia. The rings are left in place until the end of
the experiment to prevent the ring-shaped plasmodia from fus-
ing. This protocol allows us to control the geometric dimen-
sions of the annular chambers. The perimeter \(L\) (measured at
the center) of the chambers ranges from 6.0 to 13.5 cm, while
the aspect ratio \(L/e\), where \(e\) is the annulus width, ranges from
11 to 41. These high aspect ratios allow us to use a quasi one-
dimensional description of the plasmodium, parameterized by
the angle \(\theta\) (see figure 1). After punching the rings, the Petri
dish is closed and sealed again, then kept at 25 °C with heat-
ing plates. Transmitted light microscopy video is started after
a typical settling time of 15–30 min.

Two different initial configurations are prepared (and ana-
lyzed separately in section 3): either the ring-shaped plas-
modium is initially homogeneous with no visible tubular net-
work (figure 1(a)), and then we analyze how annular confine-
ment affects its formation. Or an isotropic network is already
present in the plasmodium (figure 1(b)), and then we analyze
the network reshaping induced by the sudden confinement.

Transmitted light imaging of confined plasmodia is
obtained using a Leica Z16 APO microscope. The illumina-
tion is provided by a TL5000 LED base (spectrum range: 440–
650 nm) whose intensity has been dimmed at its maximum
to ensure that it does not elicit a specific response from the
plasmodium [20]. The whole set-up is placed in a dark cham-
ber such that no other light source can alter the measurements
or the behavior of the organism. RGB images with ~500 ms
exposure time are recorded every 4 or 6 s using a CMOS Basler
color camera (acA2440-75uc). Each recording lasts between 4
and 15 h (see figure 1).

We then perform image processing to obtain an exhaust-
ive characterization of network emergence and reorganiza-
tion. Since the specimen is mostly yellow, we minimize the
computational time while maximizing the image contrast by
using only the blue channel of the RGB images. As one can
see in figures 1 and 2, the network architecture is difficult
to segment from the plasmodium because of the large range
of spatial scales it spans and the inhomogeneity of the plas-
modium thickness. Instead of using computationally expen-
sive and imperfect segmentation tools, we use coarse-grained
gradient-based orientation estimators measured at the meso-
scale (the local network architecture) to characterize it.
To quantify the emergence and directionality of the network, we compute observables derived from the components of the structure tensor. The structure tensor is well suited for detecting the average orientation of slender objects in a non-uniform background, a situation in which segmentation is difficult. The structure tensor is defined at every point \( \mathbf{x}_0 \) as:

\[
\mathbf{J}(\mathbf{x}_0) = \begin{pmatrix} \frac{I_x}{I_0} & \frac{I_{xy}}{I_0} & \frac{I_y}{I_0} \end{pmatrix},
\]

where \( I_x = \partial_x I \) and \( I_y = \partial_y I \) are the partial derivatives of the intensity \( I \) with respect to \( x \) and \( y \). The weighted averaging is defined as:

\[
\overline{w}(\mathbf{x}_0) = \int_{\mathbb{R}^2} f(\mathbf{x}) g(\mathbf{x}) w_R(\mathbf{x} - \mathbf{x}_0) \, d\mathbf{x},
\]

where \( w_R \) is a Gaussian window of radius \( R \), which defines the meso-scale size over which the estimators are defined. \( \mathbf{J} \) is a \( 2 \times 2 \) symmetric positive-definite matrix, and we note \( \lambda_M, \lambda_m \) (\( \lambda_M > \lambda_m > 0 \)) its two positive eigenvalues, defined for each position \( \mathbf{x}_0 \).

We then define the local gradient anisotropy \( E_C \) and the local gradient orientation \( \psi \) as:

\[
E_C(\mathbf{x}_0) = \lambda_M - \lambda_m,
\]

\[
\tan(2\psi(\mathbf{x}_0)) = \frac{2IT_y}{I_x^2 - I_y^2}.
\]

\( E_C \) indicates whether the local image features are oriented or not. Compared to other quantities proposed in the literature [17, 18], we found \( E_C \) to be better suited to follow the emergence of veins (comparative tests are shown in S.I. 2.3). The angle \( \psi \in [-\pi/2, +\pi/2] \) corresponds to the orientation of the eigenvector associated with \( \lambda_M \) and then indicates the main local gradient orientation. Accounting for the symmetry with respect to the radial direction, we are mainly interested in its norm \( |\psi| \). Note that the main local vein orientation is orthogonal to it.

To obtain tractable datasets, we decompose the ring in small angular sectors of uniform arc length \( s \simeq 3.3 \text{ mm} \), over which the quantities derived from the structure tensor will be averaged. Each sector is rotated as shown in figure 2 before calculating the components of \( \mathbf{J}(\mathbf{x}_0) \) within the largest rectangle inscribed in the angular sector (shown in blue in figure 2). We choose for the radius of the Gaussian weighting function \( R = \sqrt{x^2 + e^2} \), where \( e \) is the ring width, and use mirroring conditions to compute \( \mathbf{J}(\mathbf{x}_0) \) at the rectangle boundaries. Given this window size, the spatial scale over which the estimators are defined is given by the angular sector size. The values of \( |\psi| \) and \( E_C \) are then averaged over this rectangular domain, yielding a unique value per angular sector indexed by its angular position \( \theta \) (see figure 1), hereafter denoted \( |\psi|(\theta) \) and \( E_C(\theta) \) for simplicity. Finally, we define the mean vein orientation in the sector, with respect to its orhtoradial axis, as \( \alpha = \pi/2 - |\psi|(\theta) (\alpha \in [0, \pi/2]) \). An orientation \( \alpha = 0 \) (respectively \( \alpha = \pi/2 \)) corresponds to veins mainly aligned along the orhtoradial (respectively radial) direction.

This structure tensor-based image analysis is tested with regular structures of lines having radial and orhtoradial orientations. The results are detailed in S.I. 2.1.

### 3. Results

In the two subsections below we analyze separately the network evolution starting from the two initial configurations described in section 2 and illustrated in figure 1.

#### 3.1. Network emergence in confined homogeneous plasmodium

First, we analyze the emergence of the tubular network from an initially homogeneous plasmodium, quantified with the gradient anisotropy \( E_C \).

Figure 3(a) shows the space-time plot of \( E_C \) for the plasmodium shown in figure 1(a). We observe a global increase of the gradient anisotropy for all the angular positions \( \theta \), revealing the emergence of a network. It can be noticed that the pattern shows important variations between the different angular positions, suggesting that the network emergence is the result of local dynamics.

Figure 3(b) shows the typical time evolution of \( E_C \) for a given angular position \( \theta/2\pi = 0.6 \). Points corresponding to averaging over 300 s (\( 3 \) oscillation periods) have been added.
to the plot (round markers) to highlight that the trend of the curve is not affected by the thickness oscillations. On a large part of the plot, we observe an exponential increase of $E_C$ with timescale $T = 1.03 \times 10^4$ s. The experimental curve then deviates from this exponential growth, mainly due to the appearance of vein meandering (see snapshots in figure 3(b)).

Figures 3(c) and (d) show data collected from 11 different confined plasmodia with no initial network (punched from 8 different homogeneous plasmodia). Figure 3(c) shows the probability distribution of $E_C$ (scaled by its initial $\theta$-averaged value $E_C(t = 0)$), at the initial time and $3 \times 10^4$ s after. We clearly observe a large spreading of the histogram towards higher values of $E_C$. The ratio of average values is $E_C(t = 3 \times 10^4 s)/E_C(t = 0) = 2.34 \pm 0.07$ (see S.I. 3 for the estimation of the error). This confirms the global network emergence in those plasmodia.

Figure 3(d) shows the time evolution of $\bar{E_C} = \langle E_C(\theta,t)/E_C(\theta,t=0) \rangle_\theta$, the gradient anisotropy scaled by its initial value and averaged over $\theta$. Each curve corresponds to one of the 11 samples, and we limit the plots to time windows where there is no pruning, blebbing or vein meandering (see S.I. 1 and S.I. 2), resulting in time windows ranging from 2 to 10 h. We note $t_0$ the window start time. The log-linear plot confirms the exponential evolution of the gradient anisotropy. We have fitted the evolution of $\bar{E_C} = E_C(\theta,t)/E_C(\theta,t_0)$ for every angular sector of every sample with the exponential law $A \exp((t-t_0)/T)$, where $T$ and $A$ are free parameters ($A$ is limited to the range $1-\sigma_{E_C}(t_0)/E_C(\theta,t_0), 1+\sigma_{E_C}(t_0)/E_C(\theta,t_0)$), where $\sigma_{E_C}(t_0)$ is the initial standard deviation. The inset in figure 3(d) shows the histograms for the fitted values of $T$. We have distinguished values obtained for samples grown on gel with (in orange) and without (in blue) nutrients. Each point represents the value of $\bar{E_C}$ averaged over a 300 s time window. For details on the computation of the error bars, see S.I. 3. Inset: stacked histograms of fitted values of $T$ obtained for all angular sectors of every sample grown on gels with (in orange) and without (in blue) nutrients. Solid blue curve: log-normal fit of the merged histograms, with mean value $T_E = 1.7 \times 10^4$ s and standard deviation of time logarithm $\sigma = 0.7$. Lines in the main graph: exponential curves $A e^{t/T}$ with $T = T_E$ (blue dashed line), $T = \exp(\ln(T_E) - \sigma) = 0.8 \times 10^4$ s (solid black line), and $T = \exp(\ln(T_E) + \sigma) = 3.4 \times 10^4$ s (black dashed line).
section by comparing it to the network reorganization from isotropic network initial conditions.

3.2. Reshaping of confined isotropic network

We now consider plasmodia that contain an isotropic spanning network at the time they are punched with the annular walls. We use the $\alpha$ angle introduced in section 2 to quantify the local network directionality relative to the circumferential direction and to characterize the network reorganization. Figure 4(a) shows the space-time plot of $\alpha$ for the specimen shown in figure 1(b). We observe an overall decrease of $\alpha$ values over time (except close to the end of the experiments) indicating a reshaping of the network during which veins are aligning with the circumferential direction of the ring. The slight increase in $\alpha$ at the end of the experiment corresponds to the appearance of blebs and especially vein meandering. The artificial increase in $\alpha$ due to vein meandering is examined in more detail in SI 2.2. As with the network emergence studied in 3.1, the signal heterogeneity along the ring observed in figure 4(a) suggests that the network reshaping is the result of local dynamics.

For a given sample, the value of $\alpha$ averaged over the ring angular position $\theta$ is plotted in figure 4(b). The dynamics associated with network reorganization is well adjusted by an exponential decaying function, with typical timescale $T = 1.23 \times 10^5$ s, toward a small steady state value $\alpha_{\infty} \approx \min(\bar{\alpha})$. As in previous section, points corresponding to averaging over 300 s time windows ($\approx 3$ oscillation periods) have been added to the plot (round markers) to make sure that the trend of the curve is not affected by the thickness oscillations.

Figures 4(c) and (d) show the data for 7 different confined plasmodia having an initial isotropic network (punched from 6 different homogeneous plasmodia). Figure 4(c) shows the probability distribution of the network directionality $\alpha$ at $t = 0$ and $t = 14000$ s (before vein meandering) of plasmodia having initial isotropic network (IN). Distribution narrows to small $\alpha$ values as time increases. The respective average values are $\bar{\alpha}_{\text{IN}}(t = 0) = 29.8^\circ \pm 1.7^\circ$ and $\bar{\alpha}_{\text{IN}}(t = 14000) = 19.8^\circ \pm 1.3^\circ$, showing that the confinement causes the veins to align circumferentially.

In order to compare their directionality, we also reported in figure 4(c) the probability distribution of $\alpha$ measured over the 11 homogeneous plasmodia (HP) with no initial network (see section 3.1), at time $t = 14000$ s where the veins are still emerging. The distribution also peaks near $19^\circ$, confirming that veins emerge with an orientation that preferentially aligns with the circumferential direction. The average value $\bar{\alpha}_{\text{HP}}(t = 14000) = 15.5^\circ \pm 1.1^\circ$, is slightly below $\bar{\alpha}_{\text{IN}}(t = 14000)$,
suggesting that $\alpha$ has not reached its stationary value yet in the reorganizing case.

We now look at the reorganization dynamics for the 7 samples with initial isotropic networks, considering only time windows in which no blebbing or meandering occurs. As before, we note $t_0$ the initial time in such a time window. For each sample, the $\theta$-averaged value of directionality $\bar{\alpha}$ decays exponentially and is fitted with:

$$ t \rightarrow (\alpha_0 - \alpha_\infty) e^{(\alpha_0 - 1)T} + \alpha_\infty, \quad (5) $$

where $T$, $\alpha_0$ and $\alpha_\infty$ are free parameters ($\alpha_0$ and $\alpha_\infty$ values are limited to the ranges $[\bar{\alpha}(t_0) - \sigma_0, \bar{\alpha}(t_0) + \sigma_0]$ and $[\min(\bar{\alpha}) - \sigma_\infty, \min(\bar{\alpha}) + \sigma_\infty]$, where $\sigma_0$ and $\sigma_\infty$ are the respective standard deviations).

Figure 4(d) shows the time evolution $\Delta \bar{\alpha} = \bar{\alpha} - \alpha_\infty$ for the 7 samples, highlighting that their typical timescales of network reorganization are very close. The average value is $T_\alpha = (1.12 \pm 0.41) \times 10^5$ s (the error takes into account the standard deviation of the fitted timescale distribution and the median returned timescale error by the fitting procedure taking into account the propagated $\alpha$ errors). For more details on the estimation of errors, see S.I. 3. As before, we have distinguished data for samples grown on gel with (in orange) and without nutrients (in blue) to show that the presence or not of proteins does not affect the range of $T$ values.

Interestingly, the timescale $T_{\alpha}$ of network reorganization is close to the timescale $T_E$ that characterizes the network emergence, suggesting that both dynamics are driven by a common mechanism. Actually, it is worth noting that both dynamics involve transport and sol-gel transition of cytoplasm.

4. Discussion and conclusion

Using an image analysis method relying on the structure tensor, we have shown that the confinement of Physarum polycephalum plasmodia in chambers with annular geometry affects the architecture of its network: when the network is not present at the initial time, it emerges with veins preferentially aligned with the orthoradial direction. When an isotropic network exists prior to confinement, it reorganizes with orthoradial alignment of veins. The typical timescale reported for network emergence or reorganization is a few $10^4$ s, two orders of magnitude longer than the period of oscillatory contractions [8]. Confinement in annular chambers simplifies the analysis on the interplay between contractile activity, cytoplasmic flows, and network (re)shaping. In a previous study [8], we analyzed the contractile activity of confined plasmodia and noticed that contractile waves appear only 15–40 min after the formation of the ring-shaped plasmodia, and persist throughout the experiment. These contractile waves generate cytoplasmic flows [21–23], which here are oriented along the ring. Those flows in turns shape the network of veins [24, 25]. These results then indicate that contractile waves and induced cytoplasmic flows propagate along the ring before the network (re)shaping, and suggest the existence of causal relationships: geometrical confinement orients contractile patterns which orient cytoplasmic flows, which in turn orient the veins. Further experiments, e.g. with inhibitors of contractile activity, would be desirable to confirm this causal relationship.

It is noteworthy that a typical response time of 15–40 min to changes in plasmodium environment has already been reported in various contexts: for the vein reinforcement in the direction of an imposed temperature or nutrient gradient [26, 27], or the evolution of plasmodium thickness and speed oscillations [5, 8]. The ubiquity of this timescale suggests that it is characteristic of the organism in connection with its body signaling [4, 28]. In contrast, a typical response time of $10^4$ s as we found in the present study has rarely been observed: Kramar and Alim [26] noticed that the Physarum network reorganizes around a newly placed food source after 90–310 min. Akita et al [29] studied the emergence of a network from homogeneous plasmodium placed in different containers and reported a typical timescale of 2–9 h for this network emergence. Finally, Rodiek and Hauser [30] report a $10^4$ s timescale as the typical time for freely migrating microplasmodia to attain diffusive regime. Below this timescale, migration follows ballistic motion. Hence, the typical timescale for diffusive regime may be limited by the time required for the network to reorganize and adapt to a change in contractile wave direction.

The structure tensor-based image analysis appears to be a very convenient tool for detecting the emergence and alignment of the veins, but is affected by the meandering of veins in the long term. Although vein meandering has already been reported in other studies [31], its origin remains elusive so far.

Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: https://doi.org/10.17605/OSF.IO/DP58G.

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