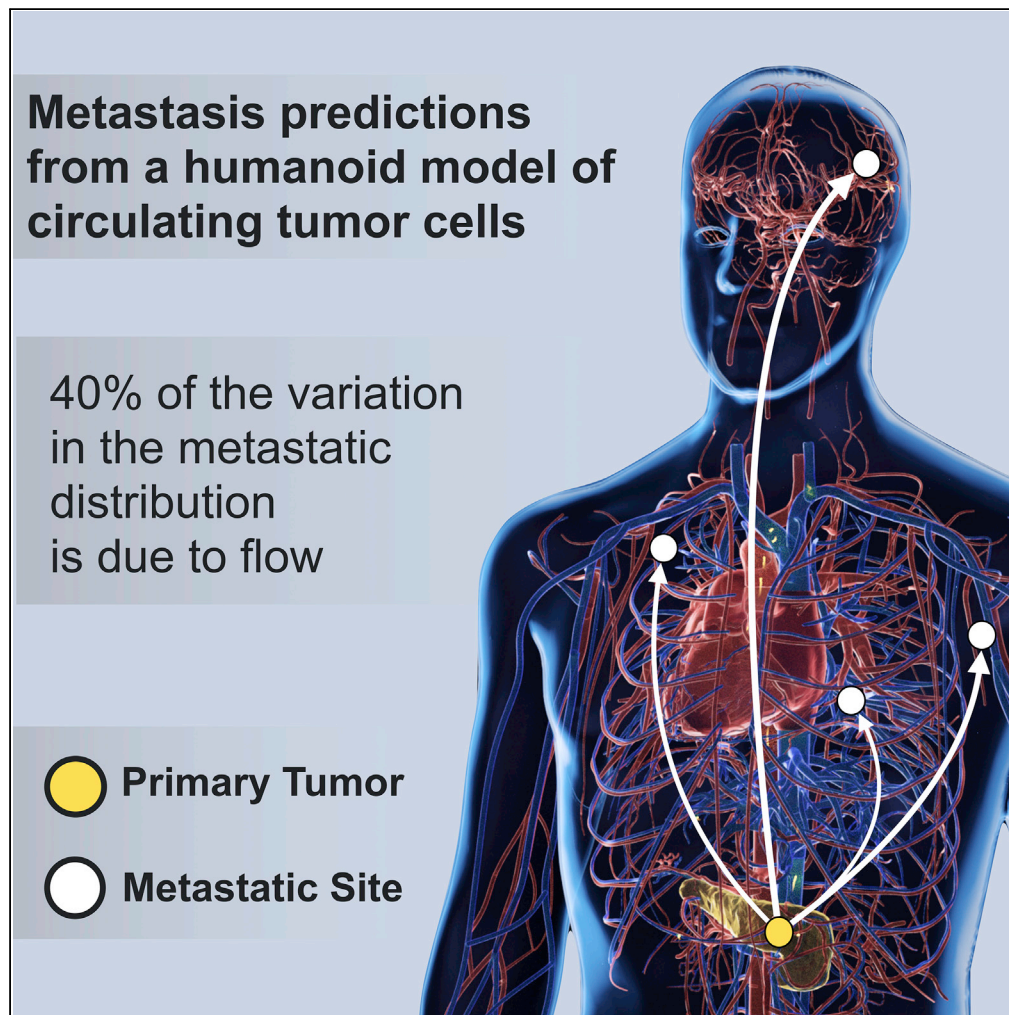


## Article

## Blood Flow Contributions to Cancer Metastasis



Francesc Font-Clos, Stefano Zapperi, Caterina A.M. La Porta

caterina.laporta@unimi.it

**HIGHLIGHTS**

We construct a high-resolution humanoid model of blood circulation

We use the model to simulate trajectories of circulating tumor cells

We compile statistics of the distribution of metastatic sites predicted by the model

Comparison with autopsies shows that flow accounts for 40% of metastasis distribution

Font-Clos et al., iScience 23, 101073  
May 22, 2020 © 2020 The Author(s).  
<https://doi.org/10.1016/j.isci.2020.101073>

## Article

Blood Flow Contributions  
to Cancer MetastasisFrancesc Font-Clos,<sup>1</sup> Stefano Zapperi,<sup>1,2</sup> and Caterina A.M. La Porta<sup>3,4,5,\*</sup>

## SUMMARY

The distribution patterns of cancer metastasis depend on a sequence of steps involving adhesion molecules and on mechanical and geometrical effects related to blood circulation, but how much each of these two aspects contributes to the metastatic spread of a specific tumor is still unknown. Here we address this question by simulating cancer cell trajectories in a high-resolution humanoid model of global blood circulation, including stochastic adhesion events, and comparing the results with the location of metastasis recorded in thousands of human autopsies for seven different solid tumors, including lung, prostate, pancreatic and colorectal cancers, showing that on average 40% of the variation in the metastatic distribution can be attributed to blood circulation. Our humanoid model of circulating tumor cells allows us to predict the metastatic spread in specific realistic conditions and can therefore guide precise therapeutic interventions to fight metastasis.

## INTRODUCTION

Cancer is the second cause of mortality worldwide, and metastasis is the main reason for patient death. The metastatic process is due to the spread of tumor cells through blood and/or lymphatic vessels and the capability of cancer cells to colonize specific sites. Already in 1889 (Paget, 1889), Paget claimed that metastasis does not occur by chance but only when tumor cells (the seeds) can adapt to a permissive microenvironment (the soil) of a given organ, as with seeds needing a fertile soil to grow and flourish. This point of view is supported by a vast literature (Fidler, 2003; Fokas et al., 2007). Later in 1929, Ewing stressed the importance for metastatic dissemination of mechanical and geometrical factors resulting from the anatomical structure of the vascular system and the associated hemodynamic flow (Ewing, 1919), a view also supported by experimental evidence (Weiss et al., 1980; Weiss, 1992) and computational models (Scott et al., 2014; Poleszczuk et al., 2016). Although both mechanical and seed-soil compatibility factors should play a role in the spread of metastasis (Chambers et al., 2002; Wirtz et al., 2011), the relative weight of each factor for a given cancer type and target organ is unknown owing to the lack of appropriate quantitative tools.

Here we build a high-resolution global blood circulation model of a humanoid male subject (Quarteroni, 2006; Müller and Toro, 2014; Blanco et al., 2014, 2015; Huang et al., 2018), including stochastic adhesion events, to simulate the trajectories of circulating tumor cells (CTCs). Using the model, we estimate the colonization patterns of CTCs at the different target organs. We compare the simulation results with a statistical analysis of thousands of human autopsies reported in the literature (Abrams et al., 1950; Disibio and French, 2008; Bubendorf et al., 2000; Budczies et al., 2015; Schlageter et al., 2016) for seven primary tumors: lung, colorectal, prostate, pancreatic, liver, kidney, esophageal, and gastric cancers. The model allows one to estimate the contribution of geometrical and flow factors to the spread of metastasis, providing an essential guidance to interpret experimental data.

## RESULTS

We build an accurate network representation of arterial and venous circulatory systems starting from a full 3D whole-body model obtained from MRI images of a male subject taken at 2-mm resolution (BodyParts3D [Mitsuhashi et al., 2009]). From this model, we extract a set of 639 artery meshes, 395 vein meshes, and 16 organ meshes, and, using graph inference algorithms, we obtain a network composed by 23,285 nodes and 23,804 edges, each annotated with their radius  $R$  and length  $L$  (see Figure 1A). A morphometric analysis of the model is summarized in Figure S1A illustrating the decrease of vessel radius as a function of the generation number (see Methods section).

Blood flow patterns are then obtained by imposing flow rate conservation at each node and a pressure boundary condition across the hearth. The pressure drop  $\Delta p$  across each vessel is proportional to the

<sup>1</sup>Center for Complexity and Biosystems, Department of Physics, University of Milan, Via Celoria 16, 20133 Milano, Italy

<sup>2</sup>CNR - Consiglio Nazionale delle Ricerche, Istituto di Chimica della Materia Condensata e di Tecnologie per l'Energia, Via R. Cozzi 53, 20125 Milano, Italy

<sup>3</sup>Center for Complexity and Biosystems, Department of Environmental Science and Policy, University of Milan, via Celoria 26, 20133 Milano, Italy

<sup>4</sup>CNR - Consiglio Nazionale delle Ricerche, Istituto di Biofisica, via Celoria 26, 20133 Milano, Italy

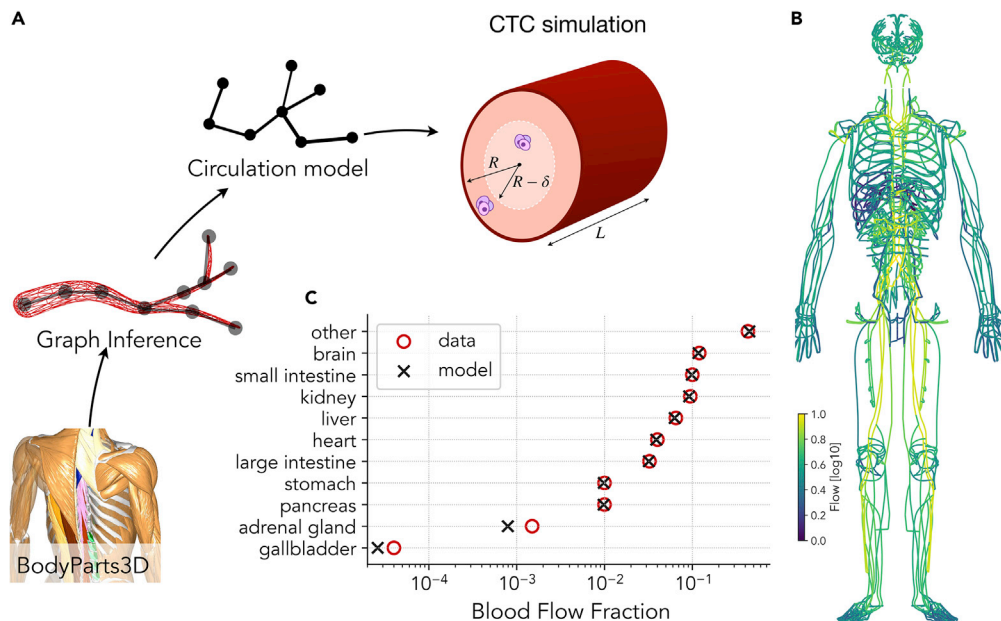
<sup>5</sup>Lead Contact

\*Correspondence:

caterina.laporta@unimi.it

<https://doi.org/10.1016/j.isci.2020.101073>





**Figure 1. Computational Model of Global Arterial-Venous Circulation Reproduces Experimentally Measured Blood Flow Distribution**

(A) The circulation network is reconstructed from the meshes obtained from a 3D body scan. The blood flow is then obtained by imposing flow conservation and the Hagen-Poiseuille equation. CTC trajectories follow the blood flow and can attach to the vessel walls if they are within a distance  $\delta$  of them.

(B) Blood flow distribution obtained from the model.

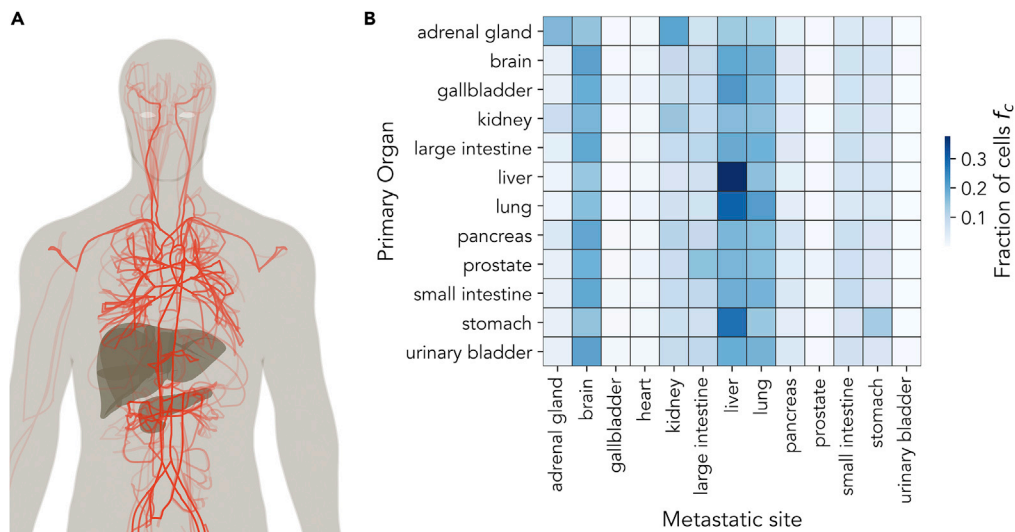
(C) The fraction of blood reaching each organ obtained with the model is in good agreement with experimental data from Williams and Leggett (1989).

flow rate  $J$  according to the Hagen-Poiseuille equation (see Figure 1A and Methods for additional details). From the solution of the hemodynamic flow equations, we compute flow distributions (Figure 1B) ensuring that the fraction of blood flow reaching each organ and the results compare well with experimental data (Figure 1C). Furthermore, the dependence of the arterial blood pressure on the vessel radius reported in Figure S1B is in agreement with physiological measurements (Guyton and Hall, 1986).

In our model, CTC trajectories are computed assuming that cancer cells are randomly released from the primary tumor and then follow the blood stream, randomly choosing the direction to take at each intersection with a probability that is proportional to the relative flow in each branch. Cancer cells can exit the blood stream with a probability that only depends on geometrical and hemodynamic factors as discussed in the Model section. Owing to computational limitations, we do not directly model the flow inside capillary beds but we estimate the probability to exit the blood stream from the typical geometry of capillary beds (see Figure S1C). In this way, the model does not consider specific microenvironmental seed-soil compatibility factors between cancer cells and target organs but only the geometry of capillary beds, where adhesion and extravasation are expected to occur. Examples of cancer cell trajectories released from the pancreas are reported in Figure 2A (see also Video S1).

Simulating the model, we collect a large set of cell trajectories starting from a predetermined set of primary tumor sites  $P$  (i.e., lung, colon, prostate, pancreas, stomach, kidney, and liver) and determine the fraction of cells  $f_c$  whose trajectory ends at a specific target organ  $O$  (including brain, liver, lungs, hearth, kidney, and pancreas). We launch a total of  $N = 10,000$  trajectories starting from each organ, let them flow along the circulatory system, and wait until they eventually stop. In this way, we can infer the distribution of metastatic dissemination expected if only flow and geometric factors were present. A summary of the simulated pattern is reported in Figure 2B, showing the probability that a primary tumor  $P$  would metastasize at organ  $O$ .

To compare our numerical estimates with real metastatic dissemination patterns, we collect data on metastasis distributions from human autopsies reported in the literature (Abrams et al., 1950; Disibio and French, 2008; Bubendorf et al., 2000; Budczies et al., 2015; Schlageter et al., 2016). We restrict our analysis to studies originating directly from



**Figure 2. Model Simulations Allow Us to Estimate the Contribution of Flow and Geometric Factors to the Metastatic Distribution**

(A) Example of 30 simulated cancer cell trajectories released from the pancreas.

(B) A color representation of the matrix, quantifying the fraction of simulated cell trajectories released from primary tumor  $P$  reaching the target organ  $O$ .

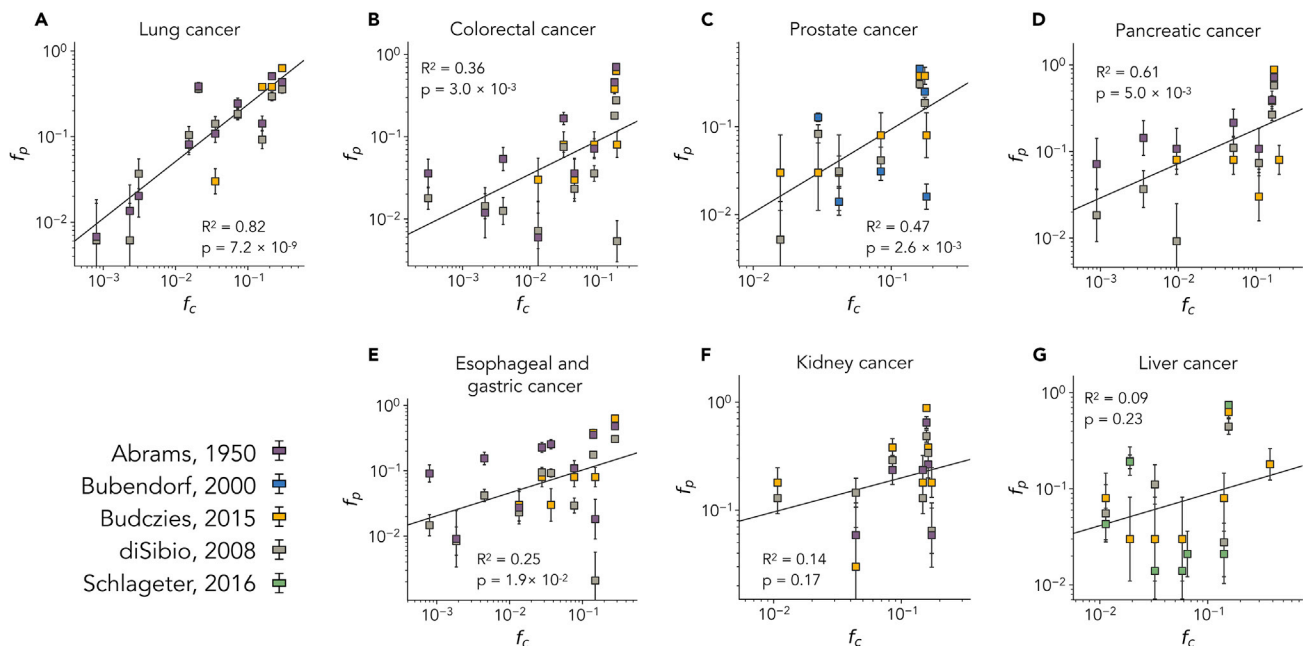
patient autopsies (Abrams et al., 1950; Disibio and French, 2008; Bubendorf et al., 2000; Budczies et al., 2015; Schlaugeter et al., 2016), disregarding other studies inferring metastatic patterns from medical records only (Chen et al., 2009; Qiu et al., 2015; Riihimäki et al., 2018). A collection of existing published data is summarized in Figures S2 and S3. For each primary tumor  $P$ , we report the fraction of patients  $f_p$  with metastasis in organ  $O$ . The data show that there is a good consistency between the value of  $f_p$  measured in different studies, taking into account expected uncertainties due to the sample size in each study. Nevertheless, we observe variations among studies that could be associated to a variety of factors intrinsic to each study, such as the location or the time at which data were gathered or the specific drug treatment of the patients. We generically refer these variations as “measurement errors.”

In Figure 3, we report a collection of cross-correlation plots of the value of  $f_c$  estimated from the model and the corresponding value of  $f_p$  measured from autopsies. The rationale behind this plot is that any variations in the metastasis distributions due to geometrical and flow effects should be due to differences in the probabilities that cancer cells reach the target organs. If these geometrical effects are prevalent, we should observe a distinct correlation between  $f_c$  and  $f_p$ . Inspection of the results reported in Figure 2 shows that most primary tumors display clear correlations between the fraction of simulated cancer cell trajectories reaching the target organs and its effective metastatic colonization as measured by autopsies. In particular, statistically significant correlations are found for lung, colorectal, prostate, pancreatic, and esophago-gastric cancers, whereas no statistically significant correlations can be found for kidney and liver cancer.

The presence of statistically significant correlations allows us also to estimate how much of the observed variations in the metastatic distribution is explained by our model. The remaining variations are due to seed-soil compatibility and to the measurement errors discussed above. This information is summarized in Figure 4A for different primary tumors. Geometrical factors result to be particularly relevant in the metastatic spread of lung cancer. Although Figure 4A is compiled from the perspective of the primary tumor, we can also take the perspective of the target organ examining the variations in the metastatic patterns with respect to the primary tumors. As shown in Figure 4B, for all the target organs considered, the variations in metastasis can be mostly attributed to seed-soil compatibility, with the possible exception of kidney metastasis, showing a significant dependence on the flow and geometric factors.

## DISCUSSION

In this paper, we have introduced a high-resolution model for the spread of CTCs through the circulatory system and used it to estimate the contribution of blood flow to metastatic spread. Our model expands the



**Figure 3. Distribution of Metastasis from Autopsies Correlates with Cancer Cell Dissemination Patterns Obtained from the Model**

Cross-correlation analysis of the fraction of patients  $f_p$  with primary tumor  $P$  and metastasis found in a distant organ  $O$  and the corresponding fraction of simulated cell trajectories  $f_c$  released from primary tumor  $P$  reaching the target organ  $O$ . Each plot corresponds to metastasis originating from a single cancer: (A) lung, (B) colorectal, (C) prostate, (D) pancreatic, (E) esophageal and gastric, (F) kidney, and (G) liver cancer. The fraction of patients  $f_p$  is obtained from different studies, as reported in the legend. Error bars are standard errors estimated using a binomial model and the sample size of each study, see methods for details. Error bars are standard errors estimated using a binomial model and the sample size of each study, see methods for details.

scope of earlier simplified models of blood circulation (Scott et al., 2014; Poleszczuk et al., 2016) by a more accurate simulation of the circulatory system. We have restricted our analysis to a set of target organs for which data were available, but our strategy is very general. Detailed statistical data on the precise localization of metastasis are unfortunately not always available. For instance, metastasis to bone and skin are usually recorded without providing information on where they occur.

In conclusion, our computational humanoid model of CTC dynamics allows simulation of the metastatic spread in a realistic geometry, including adhesion mechanisms, and can thus provide guidance for precision medicine to fight metastasis. In this context, experimental recordings of blood flow profiles by contrast-enhanced computed tomography or MRI might be used to identify future sites of metastasis that could be exploited for diagnostics and following them during treatment. Our model could also be expanded along different directions. For example, we could follow the trajectories of other relevant bodies through the circulation systems, such as atherosclerotic plaques or drug carriers.

### Limitations of the Study

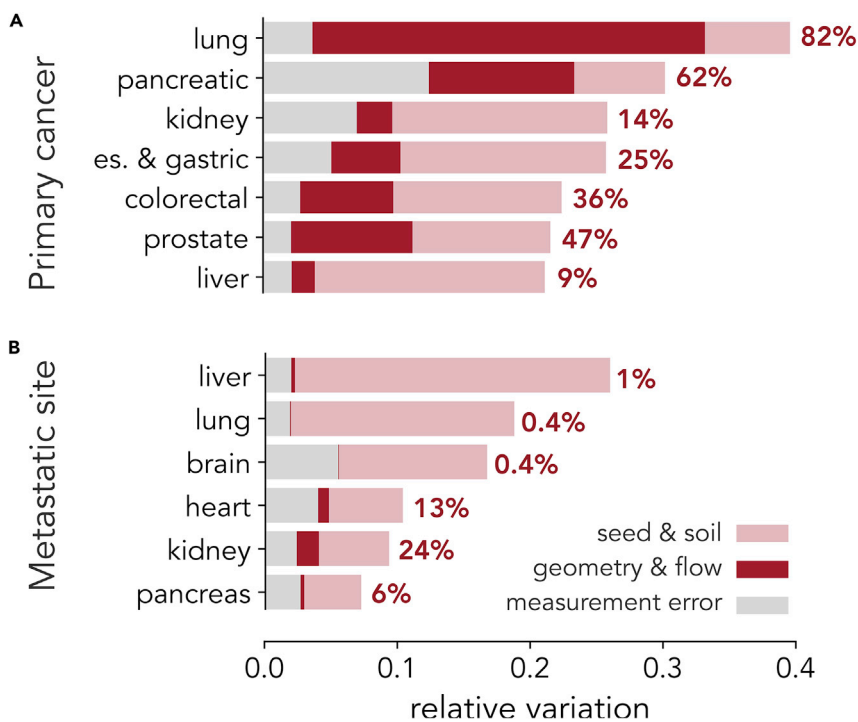
In this study we only considered blood circulation and not the lymphatic system. Therefore, we cannot describe the contribution of metastasis spreading through the lymphatic system. This might be important for tumors like melanoma. Further limitations are due to the approximations employed to simulate circulation in the veins where we did not consider valves. At the level of this study, it is not a critical limitation.

### METHODS

All methods can be found in the accompanying [Transparent Methods supplemental file](#).

### DATA AND CODE AVAILABILITY

All the simulations are performed with a custom-made Python code. A concise illustration of the algorithm, including a flowchart for the simulation of CTC trajectories, is reported in [Figure S4](#). The simulations code,



**Figure 4. Observed Variations in Metastatic Spread from a Primary Tumor Is Explained Both by “Seed and Soil” and Flow/Geometrical Mechanisms in a Tumor-Dependent Manner**

(A) Effects due to geometry and flow are found to affect considerably the observed variations in the metastatic sites reached by primary tumors. The extent of the flow contribution depends on the primary tumor and is the largest in lung cancer.

(B) The observed variations in primary tumors contributing to metastasis on a given organ is found instead to depend mostly on “seed and soil” mechanisms.

the circulation network, and all the data extracted from the literature and used to produce results and figures presented in this paper are available at <https://github.com/ComplexityBiosystems/CTC-model>.

### SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.isci.2020.101073>.

### ACKNOWLEDGMENTS

C.A.M.L.P. and S.Z. thank Ludwig-Maximilian University Munich for hospitality. S.Z. also acknowledges support from the Alexander von Humboldt Foundation through the Humboldt Research Award and thanks Friedrich-Alexander-Universität Erlangen-Nürnberg for hospitality.

### AUTHOR CONTRIBUTIONS

F.F.-C. analyzed data and performed numerical simulations. F.F.-C. and S.Z. designed the model. C.A.M.L.P. and S.Z. wrote the paper. C.A.M.L.P. designed and coordinated the project.

### DECLARATION OF INTERESTS

Authors declare no conflicts of interest.

Received: January 29, 2020

Revised: March 25, 2020

Accepted: April 14, 2020

Published: May 22, 2020

## REFERENCES

- Abrams, H.L., Spiro, R., and Goldstein, N. (1950). Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 3, 74–85.
- Blanco, P.J., Watanabe, S.M., Dari, E.A., Passos, M.A.R.F., and Feijóo, R.A. (2014). Blood flow distribution in an anatomically detailed arterial network model: criteria and algorithms. *Biomech. Model. Mechanobiol.* 13, 1303–1330.
- Blanco, P.J., Watanabe, S.M., Passos, M.A.R.F., Lemos, P.A., and Feijóo, R.A. (2015). An anatomically detailed arterial network model for one-dimensional computational hemodynamics. *IEEE Trans. Biomed. Eng.* 62, 736–753.
- Bubendorf, L., Schöpfer, A., Wagner, U., Sauter, G., Moch, H., Willi, N., Gasser, T.C., and Mihatsch, M.J. (2000). Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum. Pathol.* 31, 578–583.
- Budczies, J., von Winterfeld, M., Klauschen, F., Bockmayr, M., Lennerz, J.K., Denkert, C., Wolf, T., Warth, A., Dietel, M., Anagnostopoulos, I., et al. (2015). The landscape of metastatic progression patterns across major human cancers. *Oncotarget* 6, 570–583.
- Chambers, A.F., Groom, A.C., and MacDonald, I.C. (2002). Dissemination and growth of cancer cells in metastatic sites. *Nat. Rev. Cancer* 2, 563–572.
- Chen, L., Blumm, N., Christakis, N., Barabasi, A., and Deisboeck, T.S. (2009). Cancer metastasis networks and the prediction of progression patterns. *Br. J. Cancer* 101, 749.
- Disibio, G., and French, S.W. (2008). Metastatic patterns of cancers: results from a large autopsy study. *Arch. Pathol. Lab Med.* 132, 931–939.
- Ewing, J. (1919). *Neoplastic Diseases* (WB Saunders Company).
- Fidler, I.J. (2003). The pathogenesis of cancer metastasis: the ‘seed and soil’ hypothesis revisited. *Nat. Rev. Cancer* 3, 453–458.
- Fokas, E., Engenhardt-Cabillic, R., Daniilidis, K., Rose, F., and An, H.-X. (2007). Metastasis: the seed and soil theory gains identity. *Cancer Metastasis Rev.* 26, 705–715.
- Guyton, A.C., and Hall, J.E. (1986). *Textbook of Medical Physiology*, Vol. 548 (Saunders), pp. 157–166.
- Huang, G.P., Yu, H., Yang, Z., Schwieterman, R., and Ludwig, B. (2018). 1D simulation of blood flow characteristics in the circle of willis using THINkS. *Comput. Methods Biomech. Biomed. Engin.* 21, 389–397.
- Mitsuhashi, N., Fujieda, K., Tamura, T., Kawamoto, S., Takagi, T., and Okubo, K. (2009). BodyParts3D: 3D structure database for anatomical concepts. *Nucleic Acids Res.* 37, D782–D785.
- Müller, L.O., and Toro, E.F. (2014). A global multiscale mathematical model for the human circulation with emphasis on the venous system. *Int. J. Numer. Method Biomed. Eng.* 30, 681–725.
- Paget, S. (1889). The distribution of secondary growths in cancer of the breast. *Lancet* 133, 571–573.
- Poleszczuk, J.T., Luddy, K.A., Prokopiou, S., Robertson-Tessi, M., Moros, E.G., Fishman, M., Djeu, J.Y., Finkelstein, S.E., and Enderling, H. (2016). Abscopal benefits of localized radiotherapy depend on activated t-cell trafficking and distribution between metastatic lesions. *Cancer Res.* 76, 1009–1018.
- Qiu, M., Hu, J., Yang, D., Cosgrove, D.P., and Xu, R. (2015). Pattern of distant metastases in colorectal cancer: a seer based study. *Oncotarget* 6, 38658.
- Quarteroni, A. (2006). *What Mathematics Can Do For the Simulation of Blood Circulation* (MOX Report).
- Riihimäki, M., Thomsen, H., Sundquist, K., Sundquist, J., and Hemminki, K. (2018). Clinical landscape of cancer metastases. *Cancer Med.* 7, 5534–5542.
- Schlageter, M., Quagliata, L., Matter, M., Perrina, V., Tomillo, L., and Terracciano, L. (2016). Clinicopathological features and metastatic pattern of hepatocellular carcinoma: an autopsy study of 398 patients. *Pathobiology* 83, 301–307.
- Scott, J.G., Fletcher, A.G., Maini, P.K., Anderson, A.R.A., and Gerlee, P. (2014). A filter-flow perspective of haematogenous metastasis offers a non-genetic paradigm for personalised cancer therapy. *Eur. J. Cancer* 50, 3068–3075.
- Weiss, L. (1992). Comments on hematogenous metastatic patterns in humans as revealed by autopsy. *Clin. Exp. Metastasis* 10, 191–199.
- Weiss, L., Haydock, K., Pickren, J.W., and Lane, W.W. (1980). Organ vascularity and metastatic frequency. *Am. J. Pathol.* 101, 101–113.
- Williams, L.R., and Leggett, R.W. (1989). Reference values for resting blood flow to organs of man. *Clin. Phys. Physiol. Meas.* 10, 187–217.
- Wirtz, D., Konstantopoulos, K., and Searson, P.C. (2011). The physics of cancer: the role of physical interactions and mechanical forces in metastasis. *Nat. Rev. Cancer* 11, 512.

**iScience, Volume 23**

**Supplemental Information**

**Blood Flow Contributions  
to Cancer Metastasis**

**Francesc Font-Clos, Stefano Zapperi, and Caterina A.M. La Porta**



# Supplemental Information: Blood flow contributions to cancer metastasis

Francesco Font-Clos<sup>a</sup>, Stefano Zapperi<sup>a,b</sup>, Caterina A. M. La Porta<sup>c,d,\*</sup>

<sup>a</sup>*Center for Complexity and Biosystems, Department of Physics, University of Milan, Via Celoria 16, 20133 Milano, Italy*

<sup>b</sup>*CNR - Consiglio Nazionale delle Ricerche, Istituto di Chimica della Materia Condensata e di Tecnologie per l'Energia, Via R. Cozzi 53, 20125 Milano, Italy*

<sup>c</sup>*Center for Complexity and Biosystems, Department of Environmental Science and Policy, University of Milan, via Celoria 26, 20133 Milano, Italy*

<sup>d</sup>*CNR - Consiglio Nazionale delle Ricerche, Istituto di Biofisica, via Celoria 26, 20133 Milano, Italy*

---

---

## Transparent Methods

### *Anatomical data*

To build an accurate network representation of arterial and venous circulatory systems, we use data from the Anatomography project, using its underlying dataset, BodyParts3D (Mitsuhashi et al., 2009), a set of 2234 mesh files covering a full 3D whole-body model obtained from 2mm interval magnetic resonance imaging (MRI) images of a male subject. Each mesh file is associated with terms from the Foundation Model of Anatomy (FMA), a domain ontology of anatomical knowledge. Using FMA terms, we are able to locate 639 mesh files corresponding to the arterial circulatory system (keywords: artery, arteries, arterial, aorta) and 395 mesh files corresponding to the venous circulatory system (keywords: vein, veins, venous, cava). We subdivide each mesh into its connected components, obtaining 1319 meshes, and remove 53 duplicated meshes. In summary, we retrieve a total of 1266 mesh files from the BodyParts3D dataset that cover the full circulatory system. We also locate 16 meshes that correspond to the following body organs: brain, large intestine, small intestine, left lung, right lung, pancreas, stomach, heart, left kidney, right kidney, liver, prostate, gallbladder, urinary bladder, left adrenal gland and right adrenal gland.

### *3D mesh to graph conversion*

In order to transform a mesh into a graph (see Fig. 1a), we use Elastic Principal Graph (EIPiGraph) (Albergante et al., 2018), a manifold learning algorithm originally designed to infer branching trajectories in single-cell datasets. Specifically, we sample 5000 points uniformly across the surface of the mesh and feed those to EIPiGraph. We manually verify that the obtained graph corresponds to the correct topological structure of the mesh. In cases of meshes with complicated geometry, however, EIPiGraph fails to

---

\*Corresponding author: caterina.laporta@unimi.it

obtain the correct graph. To tackle those cases, we split the mesh into two pieces using the sign of its first principal component, obtaining two submeshes with simpler geometry. We iterate this process until all submeshes can be correctly transformed into a graph using ELPiGraph, and reconstruct the graph of the original mesh by joining the obtained graphs along the planes that were used to split the mesh. In addition, we measure the radius of the vessel at each edge by fitting the smallest possible circumference centered at the middle point of the edge. In summary, for each 3D-mesh we obtain a graph whose nodes have an associated position and whose edges have an associated radius.

#### *Construction of the full-body graph*

We merge the 1266 graphs obtained from BodyParts3D mesh files to obtain a single full-body graph composed of 23285 nodes and 23804 edges. The details of the graph-merging process are as follows: first, we automatically join graphs whose associated meshes have non-null intersection through their closest nodes. Then, we manually verify them by visualizing their associated meshes, making sure they correspond to anatomically connected vessels and removing the connection when that is not the case. While for small vessels in some cases it is difficult to assert if two graphs should be connected or not, we take special care when dealing with major arteries and veins, and have verified that the main known circulatory paths are correctly assembled in the final whole-body graph. Finally, we add nodes representing the body organs for which a mesh file is available, and connect them to nodes that verify one of the two following conditions: (1) they are inside the mesh of the organ, or (2) they are at a distance of less than 10mm from the organ. The distance between an organ and a node is computed as the shortest distance between the node and any vertex of the mesh of the organ. The BodyParts3D mesh files are incomplete, particularly for the head section which lacks all the venous system and parts of the common carotid arteries, connecting the head to the neck. We thus reconnect the left and right common carotid arteries to the corresponding internal and external carotid arteries. It is less straightforward to replace the missing veins, but we can not disregard completely the veins in the head because this would lead to incorrect global flow patterns. We solve this problem by adding a set of effective head vessels, tuning their flow resistance so that systemic circulation is accurately reproduced.

#### *Solution to hemodynamic flow equations*

We assume that blood is a Newtonian fluid of constant viscosity and that vessels are essentially non-deformable, which is a good approximation for large and medium size vessels (Quarteroni, 2006). Pressure changes due to the systole and diastole periods during a full cardiac cycle are not included in the model. We assume a constant mean arterial pressure of 100 mmHg for the main circulatory system and 14 mmHg for the pulmonary circulatory system. This approximation is justified since the cardiac cycle occurs in a timescale of the order of seconds, while we are interested in metastatic patterns of CTCs, happening in the course of much larger timescales. Furthermore, given that the dynamics of our simulated cancer cell trajectories depend on ratios of blood flow rates, and not on their absolute values, the fraction of cells measured in simulations is effectively independent of the pressure and viscosity values. Finally, to account for the effect of the vessels not included in the original mesh data, we add resistive elements at the arterial-to-venous connections. We use the Powell method as implemented in the

scientific python library `scipy` (Jones et al., 2001) and data from (Williams and Leggett, 1989) to adjust the effective resistance of these connections, guaranteeing a realistic blood flow distribution, as shown in Fig. 1.

Under those assumptions, we consider a system of hemodynamic flow equations on a network of  $N$  nodes, divided into  $B$  leaf nodes and  $N - B$  internal nodes. Our setup considers (i) flow conservation for all internal nodes and (ii) the Hagen-Poiseuille equation for all edges. For a given edge  $(i, j)$ , the Hagen-Poiseuille equation reads:

$$J_{ij} = \frac{\pi \Delta p_{ij} R_{ij}^4}{8\eta L_{ij}} \quad (1)$$

where  $J_{ij}$  stands for the flow rate along edge  $(i, j)$ ,  $R_{ij}$  is the measured radius of the edge,  $L_{ij}$  its length and  $\eta$  the viscosity of the fluid, which we assume constant. The pressure difference  $\Delta p_{ij}$  is simply

$$\Delta p_{ij} = p_j - p_i \quad (2)$$

with  $p_i, p_j$  the pressure at nodes  $i$  and  $j$ . We impose blood flow conservation for all internal nodes  $i$ ,

$$\sum_j J_{ij} = 0, \quad i = 1 \dots N - B \quad (3)$$

and set boundary conditions for the pressure of the remaining  $B$  leaf nodes, which correspond to connections to/from the heart. Combining these three equations we obtain a linear system of equations,

$$\sum_j \frac{\pi(p_j - p_i)R_{ij}^4}{8\eta L_{ij}} = 0, \quad i = 1 \dots N, \quad (4)$$

Given that the values of  $R_{ij}$  and  $L_{ij}$  are known, and that the pressure of  $B$  nodes is fixed by boundary conditions, we are left with  $N - B$  variables and  $N - B$  linear constraints. The topology of the network ensures that the system has a solution, which we find using the `sparse.linalg.sparse_inv` function from the scientific python library `scipy` (Jones et al., 2001). Finally, we calculate the flux along the edges  $J_{ij}$  by inserting the obtained pressure values  $p_i$  into Eq. (1). We solve the system separately for the main circulatory system and the pulmonary circulatory system to allow for realistic different pressure differences on each system when setting boundary conditions. In simulating venous circulation, we do not consider the presence of valves.

#### *Simulation of cancer cell trajectories*

We simulate cancer cell trajectories assuming that cancer cells follow the blood flow. To simulate metastasis stemming from a given primary tumor, cells are initially released from random nodes belonging to the relevant body organ. At branching points, cells choose which branch to take with probabilities proportional to the blood flow of each branch. That is, given a node  $i$  with  $j = 1 \dots k_i$  outgoing edges, the probability for a cancer cell to choose edge  $j$  is given by

$$P_{i \rightarrow j} = \frac{J_{ij}}{\sum_j J_{ij}} \quad (5)$$

where  $J_{ij}$  is the blood flux along edge  $(i, j)$ . Cell trajectories start from nodes that are closer than 10 mm from a given organ and follow the blood flow as described. We also assume that cells can enter into capillary beds with rate  $\epsilon$  only if found at a distance less than  $\delta$  from the wall, while they can not enter otherwise (see Fig. 1). When cells reach the outlet of an artery and do not attach to the capillary bed, they are re-inserted in the nearest node in venous system. For a short vessel segment, blood flow can be approximated by the equations of laminar flow in a tube (Glaser, 1999). In this case, the velocity profile  $v(r)$  in a tube of radius  $R$  and length  $L$  is known to be of parabolic type,

$$v(r) = \frac{\Delta p}{4L\nu}(R^2 - r^2), \quad (6)$$

We use this expression to compute the probability  $P_{\text{wall}}$  that a cell flowing along the blood stream is at a distance less than  $\delta$  from the wall of a vessel of radius  $R$ :

$$P_{\text{wall}} = \frac{\int_0^{2\pi} d\theta \int_{R-\delta}^R dr r v(r)}{\int_0^{2\pi} d\theta \int_0^R dr r v(r)} \simeq \frac{4\delta^2}{R^2} \quad (7)$$

Multiplying then by the rate  $\epsilon$ , we obtain an expression for the rate for a cell to enter into a capillary bed from a vessel of radius  $R$ :

$$P_{\text{exit}}(R) = P_{\text{wall}} \cdot \epsilon = \frac{4\delta^2\epsilon}{R^2} \quad (8)$$

This expression accounts for the possibility that cancer cells enters into a capillary bed and reflects the fact that when going through large vessels, cells are less likely to be near the walls and thus less likely to enter into capillaries. The value of  $\epsilon$  would in principle depend on the properties of tumor cells, while the value of  $\delta$  could be related to the size of circulating tumor cells and the clusters they form. We do not model these aspects in this work, since our aim is to disentangle seed-soil versus geometry and flow contributions to cancer metastasis incidence rates. We thus choose both  $\delta$  and  $\epsilon$  to be constant across the vascular system.

#### *Cell attachment in capillary beds*

Once a CTC enters into a capillary bed, we can estimate the probability of extravasation to seed a new metastasis. To this end, we model capillary beds as binary trees obeying on Murray's law (Welter and Rieger, 2010) which states that if a vessel of radius  $R$  splits in two vessels of radii  $R_a$  and  $R_b$ , then  $R^3 = R_a^3 + R_b^3$  (Murray, 1926). If the inlet to the capillary bed has radius  $R_0$  and  $R_a = R_b$ , after  $n$  bifurcations the capillary radius  $R_n$  is given by (Sherman, 1981)

$$R_n = 2^{-1/3} R_{n-1} = \dots = 2^{-n/3} R_0, \quad (9)$$

Furthermore, we assume that the lengths of the vessel are proportional to their radius  $L_n = \alpha R_n$ , as suggested by morphometric data Huang et al. (1996). To obtain the total number of bifurcations  $N$  in a capillary bed, we set  $R_N = 3.5\mu\text{m}$ , based on the observation that the smallest capillaries have a diameter of 5 – 10 $\mu\text{m}$  Mittal et al. (2005); Chan et al. (2012). Then using Eq. 9, we obtain

$$N = 3 \log_2 \left( \frac{R_0}{R_N} \right) \quad (10)$$

We next assume that the attachment probability while traversing a capillary in the tree is proportional to Eq. 8 multiplied by the time spent in the capillary. Since the flow after each bifurcation is conserved (i.e.  $Q_n = 2Q_{n+1}$ ) in a *Murray's tree*, the time  $T_n$  to traverse a capillary at generation  $n$  is independent of  $n$ . Therefore, the probability of attaching while traversing the  $n$ -th generation of the tree is simply given by:

$$P(n) = C/R_n^2 \quad (11)$$

The total probability of attachment while traversing the whole tree can be approximated as follows:

$$P_{\text{ATT}} = 1 - \prod_{n=1}^N (1 - P(n)) \simeq 1 - \exp\left(-\sum_{n=1}^N P(n)\right) \quad (12)$$

where the approximation is valid as long as  $P(n)$  is small. Now the sum can be evaluated explicitly,

$$\sum_{n=1}^N P(n) = \sum_{n=1}^N \left(\frac{C}{R_0^2}\right) 2^{2n/3} \quad (13)$$

$$= \frac{C}{R_0^2} \sum_{n=1}^N \left(2^{2/3}\right)^n \quad (14)$$

$$= \frac{C}{R_0^2} \frac{2^{2/3} (2^{2N/3} - 1)}{2^{2/3} - 1} \quad (15)$$

substituting eq. (10) back and condensing all the prefactors into a single constant  $C_0$ , we obtain

$$\sum_{n=1}^N P(n) = \frac{C_0}{R_0^2} \left(\frac{R_0^2}{R_N^2} - 1\right) = C_0 \left(\frac{1}{R_N^2} - \frac{1}{R_0^2}\right) \quad (16)$$

so that the attachment probability for a tree of inlet radius  $R_0$  is approximately given by

$$P_{\text{ATT}} \simeq 1 - \exp\left(-C_0 \left(\frac{1}{R_N^2} - \frac{1}{R_0^2}\right)\right). \quad (17)$$

In the simulations, we chose the inlet radii to be  $R_0 = 100\mu\text{m}$ , except for vessels whose radius is already smaller than  $R_0$  where we use the vessel radius itself. Finally, we set  $C_0 = 10^{-2}\text{mm}^2$ .

### *Morphometric analysis*

We define the number of generations from any vessel segment to the heart as the number of branching points along the shortest path. The shortest path is computed using the metric distance along it via the `networkx` python library. For capillaries, the total number of generations is computed as the number of generations to the heart plus the number of generations given in Eq. 10. Fig S1(d) shows the distribution of total number of generations, whose median value 31.7 is in agreement with known morphometric measurements (Huang et al., 1996; Mittal et al., 2005).

### Datasets

We collect data on frequency of metastasis among different primary tumors and corresponding metastatic sites from 5 large autopsy studies: **1. (Abrams, 1950)** Study of 1000 epithelial malignant neoplasm cases, autopsied at Montefiore Hospital, New York, between 1943 and 1947 (Abrams et al., 1950). We collect the tabulated data of frequency of metastasis among 39 metastatic sites for 167 breast cancer cases, 118 colon cancer cases, 34 kidney cancer cases, 64 ovary cancer cases, 32 pancreatic cancer cases, 87 rectum cancer cases and 119 gastric cancer cases. The colorectal data displayed in Fig. S3 are obtained pulling together colon and rectum cases. **2. (Bubendorf, 2000)** Study of 1589 prostate cancer cases, autopsied at the Institute of Pathology of the University of Basel between 1967 and 1995, of which 556 reveal hematogeneous metastasis over 17 different metastatic sites (Bubendorf et al., 2000). **3. (diSibio, 2008)** Review study of data from 3827 autopsies performed between 1914 and 1943 at 5 different medical centers in the state of Massachusetts (Disibio and French, 2008). The study includes data for 41 primary tumors and 30 different metastatic sites. We collect tabulated metastasis frequency data for 437 rectum cancer cases, 432 breast cancer cases, 418 cervix cancer cases, 348 gastric cancer cases, 193 prostate cancer cases, 183 bladder cancer cases, 165 tongue cancer cases, 163 lung cancer cases, 129 esophageal cancer cases, 123 colon cancer cases, 120 uterus cancer cases, 117 pharynx cancer cases, 109 pancreatic cancer cases and 28 other primary tumors with less than 100 cases. The colorectal and gastric and esophageal data displayed in Fig S3 are obtained pulling together colon and rectum cases and gastric and esophageal cases, respectively. **4. (Budczies, 2015)** Study of 1008 cancer cases with metastatic solid malignancies autopsied at the Charité Institute of Pathology, Berlin, between 2000 and 2013 (Budczies et al., 2015). The study comprises 16 different primary tumors and records 20 different metastatic sites. We collect values for relative frequency of metastasis from the main text in some cases, and infer the rest from their Figure 3A, for 280 lung cancer cases, 98 esophageal and gastric cancer cases, 89 breast cancer cases, 89 colorectal cancer cases, 78 pancreatic cancer cases, 71 biliary cancer cases, 48 head and neck cancer cases, 46 kidney cancer cases, 40 neuroendocrine cancer cases, 33 prostate cancer cases, 32 liver cancer cases and 4 other primary tumors with less than 30 cases. **5. (Schlageter, 2016)** Study of 398 hepatocellular carcinoma cases autopsied at the Institute of Pathology, Basel, between 1969 and 1983 and between 1988 and 2012 (Schlageter et al., 2016). The study records 11 different metastatic sites.

### Computation of corrected $r^2$ values

The regression lines and corresponding  $r^2$  values in Fig. 3 are computed in logarithmic space and taking into account measurement errors in the metastatic frequency data. We limit ourselves to combinations of primary tumor and metastatic site for which at least two independent studies are available. To compute regression in logarithmic space, we consider the standard linear regression equation,  $\hat{y} = \alpha x + \beta$  with  $x = \log(f_c)$  the logarithm of the fraction of cells obtained from the circulation model,  $y = \log(f_p)$  the logarithm of the fraction of patients obtained from the literature and  $\hat{y} = \alpha \log(f_c) + \beta$  the linear regression estimation. After fitting the slope  $\alpha$  and intercept  $\beta$  using the stats.linregress function from the scientific python library scipy (Jones et al., 2001), we compute the corrected explained variance ratio  $r^2$ ,

$$r^2 = \frac{S^2 - E^2}{S^2 - e^2}. \quad (18)$$

Notice how this calculation differs from the more usual  $R^2$  one in that the denominator of Eq. (18) has an additional  $-e^2$  term that accounts for measurement errors. In this expression  $E^2$ ,  $S^2$  and  $e^2$  are defined as follows:

$$E^2 = \frac{1}{N} \sum_i (\hat{y}_i - y_i)^2 \quad (19)$$

$$S^2 = \frac{1}{N} \sum_i (y_i - \bar{y})^2 \quad (20)$$

$$e^2 = \frac{1}{N} \sum_i \sigma_{y_i}^2 \quad (21)$$

The logarithmic measurement errors  $\sigma_y$  are computed from the linear measurement errors  $\sigma_{f_p}$  via the error propagation formula,

$$\sigma_y = \left| \frac{\sigma_{f_p}}{f_p} \right|. \quad (22)$$

Linear measurement errors are inferred from the number of patients  $N_p$  of each dataset assuming a binomial model,

$$\sigma_{f_p} = \sqrt{\frac{f_p(1-f_p)}{N_p}}. \quad (23)$$

#### *Decomposition of variability of metastasis incidence rate*

The values of  $S^2$ ,  $E^2$  and  $e^2$  are also used in Fig. 4 to decompose the total variability of metastasis incidence rates  $S^2$  into three pieces:

$$S^2 = \underbrace{(S^2 - E^2)}_{\text{geom \& flow}} + \underbrace{(E^2 - e^2)}_{\text{seed \& soil}} + \underbrace{(e^2)}_{\text{measurement}} \quad (24)$$

Given that our model is based on geometry and flow and does not incorporate any specific target-organ compatibility factors, these three terms can be interpreted in terms of seed & soil and geometry & flow hypothesis:  $S^2 - E^2$  is the variability of the data that the model can account for, and hence is attributed to the geometry and flow hypothesis;  $E^2 - e^2$  is the variability of the data that the model cannot account for after taking into account measurement errors, and is attributed to the seed and soil hypothesis; and  $e^2$  is by definition the measurement error of the data.

#### *Data and code availability*

All code and data necessary to reproduce the results and figures of this paper are available at <https://github.com/ComplexityBiosystems/CTC-model>. This includes the circulatory network, python code to simulate CTC trajectories, and the autopsy data extracted from the literature.

## Supplemental references

- Abrams, H. L., Spiro, R., Goldstein, N., Jan 1950. Metastases in carcinoma; analysis of 1000 autopsied cases. *Cancer* 3 (1), 74–85.
- Albergante, L., Mirkes, E. M., Chen, H., Martin, A., Faure, L., Barillot, E., Pinello, L., Gorban, A. N., Zinovyev, A., Apr. 2018. Robust and scalable learning of complex dataset topologies via elpigraph.
- Bubendorf, L., Schöpfer, A., Wagner, U., Sauter, G., Moch, H., Willi, N., Gasser, T. C., Mihatsch, M. J., May 2000. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol* 31 (5), 578–83.
- Budczies, J., von Winterfeld, M., Klauschen, F., Bockmayr, M., Lennerz, J. K., Denkert, C., Wolf, T., Warth, A., Dietel, M., Anagnostopoulos, I., Weichert, W., Wittschieber, D., Stenzinger, A., Jan 2015. The landscape of metastatic progression patterns across major human cancers. *Oncotarget* 6 (1), 570–83.
- Chan, G., Balaratnasingam, C., Paula, K. Y., Morgan, W. H., McAllister, I. L., Cringle, S. J., Yu, D.-Y., 2012. Quantitative morphometry of perifoveal capillary networks in the human retina. *Investigative ophthalmology & visual science* 53 (9), 5502–5514.
- Disibio, G., French, S. W., Jun 2008. Metastatic patterns of cancers: results from a large autopsy study. *Arch Pathol Lab Med* 132 (6), 931–9.
- Glaser, R., 1999. *Biophysics*, 1st Edition. Springer-Verlag Berlin Heidelberg.
- Huang, W., Yen, R. T., McLaurine, M., Bledsoe, G., Nov 1996. Morphometry of the human pulmonary vasculature. *J Appl Physiol* (1985) 81 (5), 2123–33.
- Jones, E., Oliphant, T., Peterson, P., et al., 2001. SciPy: Open source scientific tools for Python. [Http://www.scipy.org/](http://www.scipy.org/).  
URL <http://www.scipy.org/>
- Mitsubishi, N., Fujieda, K., Tamura, T., Kawamoto, S., Takagi, T., Okubo, K., Jan. 2009. BodyParts3D: 3D structure database for anatomical concepts. *Nucleic Acids Res.* 37 (Database issue), D782–5.
- Mittal, N., Zhou, Y., Ung, S., Linares, C., Molloy, S., Kassab, G. S., Aug 2005. A computer reconstruction of the entire coronary arterial tree based on detailed morphometric data. *Ann Biomed Eng* 33 (8), 1015–26.
- Murray, C. D., 1926. The physiological principle of minimum work: I. the vascular system and the cost of blood volume. *Proceedings of the National Academy of Sciences of the United States of America* 12 (3), 207.
- Quarteroni, A., 2006. What mathematics can do for the simulation of blood circulation. *MOX Report*.
- Schlageter, M., Quagliata, L., Matter, M., Perrina, V., Tornillo, L., Terracciano, L., 2016. Clinicopathological features and metastatic pattern of hepatocellular carcinoma: An autopsy study of 398 patients. *Pathobiology* 83 (6), 301–7.
- Sherman, T. F., 1981. On connecting large vessels to small. the meaning of murray’s law. *The Journal of general physiology* 78 (4), 431–453.
- Welter, M., Rieger, H., 2010. Physical determinants of vascular network remodeling during tumor growth. *The European Physical Journal E* 33 (2), 149–163.
- Williams, L. R., Leggett, R. W., Aug. 1989. Reference values for resting blood flow to organs of man. *Clin. Phys. Physiol. Meas.* 10 (3), 187–217.



## Supplemental figures

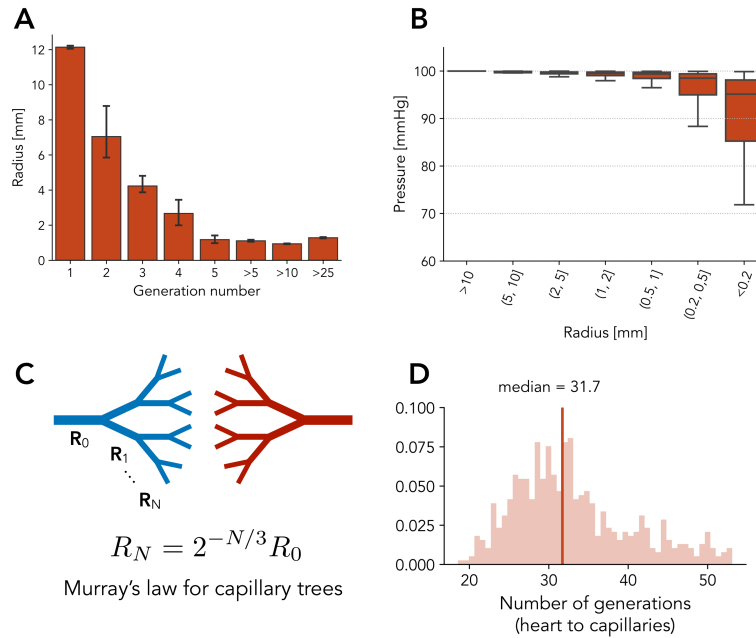


Figure S1: **Morphological details for the MRI-derived circulatory network model. Related to Fig. 1.** (a) Measured radii as a function of generation number, defined as the number of branching points from a vessel segment to the heart. The panel shows that vessels further away from the heart tend to be thinner, as expected. (b) Mean arterial pressure (MAP) obtained solving the blood flow equations, as a function of the radius of arterial vessels. The pressure at the heart is fixed to 100 mmHg. The panel shows that in the range 10 to 1 mm, pressure is maintained close to 100 mmHg, displaying only a mild drop with decreasing radius as expected. For very small vessels of radii below 0.5 mm, we observe instead a larger pressure drop. (c) Schematic representation of our modeling of capillary beds using Murray's law. (d) Distribution of the number of generations from heart to capillaries. Generations are defined as number of branching points along a shortest path.

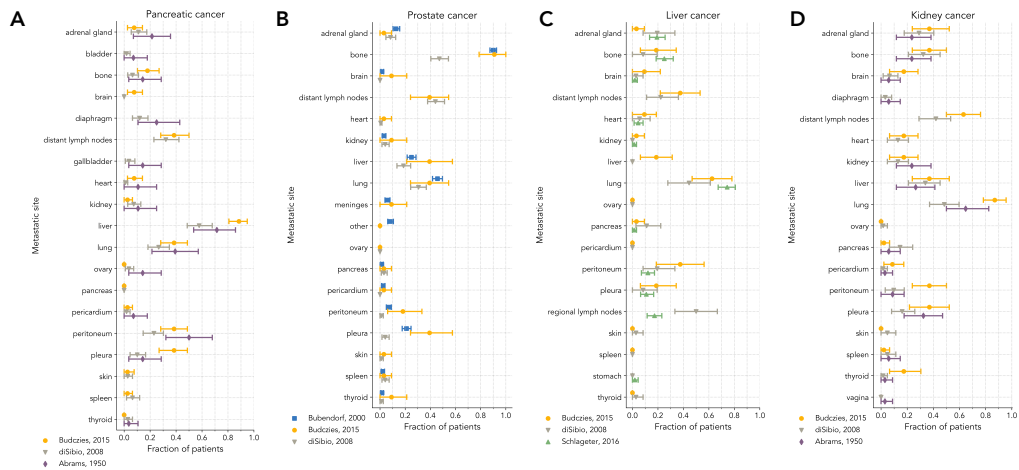


Figure S2: **Statistics of data from autopsies (First part).** Related to Fig. 3. A compilation of the values of  $f_p$  — the fraction of patients with a given primary tumor and metastasis found in a distant organ — obtained from autopsy data reported in the literature for a) pancreatic cancer, b) prostate cancer, c) liver cancer and d) kidney cancer. Error bars are standard errors estimated using a binomial model and the sample size of each study, see methods for details.

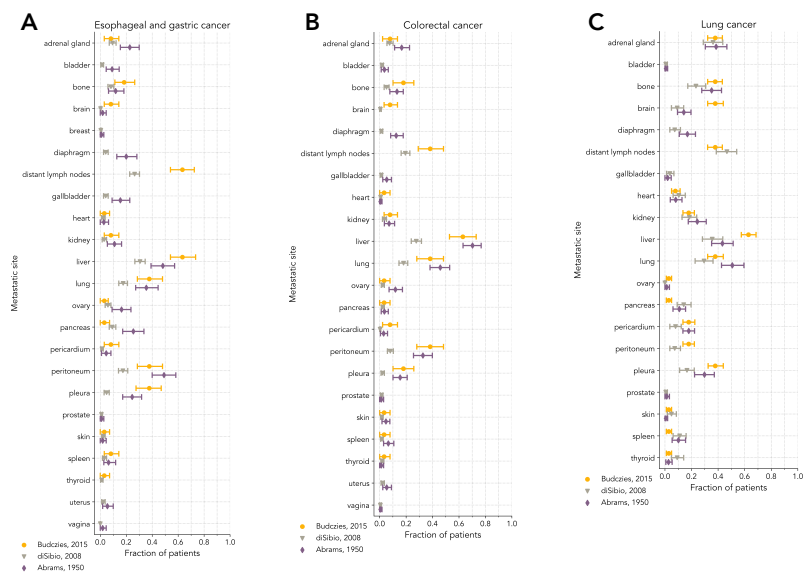


Figure S3: **Statistics of data from autopsies (Second part).** Related to Fig. 3. A compilation of the values of  $f_p$  — the fraction of patients with a given primary tumor and metastasis found in a distant organ — obtained from autopsy data reported in the literature for a) esophageal and gastric cancer, b) colorectal cancer and c) lung cancer. Error bars are standard errors estimated using a binomial model and the sample size of each study, see methods for details.

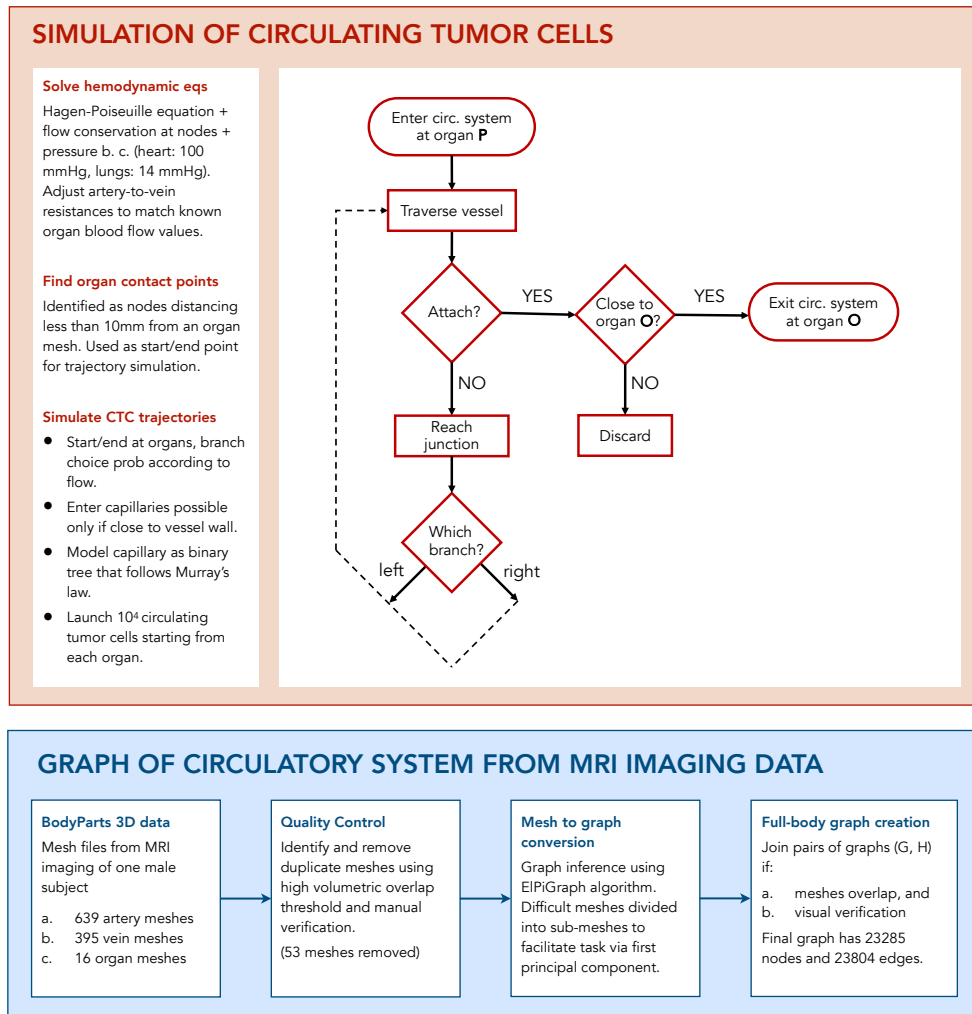


Figure S4: A schematic description of the algorithms used for the simulations. Related to Fig. 2.