**Supplementary File S1.**

**Implementation of the Model**

We used BioNetGen1, a rule-based approach, to generate the model, which provides great help in models that involve dynamic assembly of multi-protein complexes. Our model is a whole-body model incorporating VEGF transport and kinetics, as well as the transport and kinetics of TSP1. We included all the significant species, which are shown in Fig. 1. The seed species and reaction rules are defined in BioNetGen, the rule-based modeling framework. These defined 86 seed species (29 in normal, 28 in blood, and 29 in tumor) participate in 452 reaction rules (129 in normal, 184 in blood, and 139 in tumor). Because of the numerous multi-species complexes, the 452 reaction rules and 86 seed species produce a total of 561 species and 2618 reactions. It is worth noting that this large number of species is due to the formation of complexes of species and the propagation of the reactions, of which some are highly similar and do not affect the soundness of the model. In the end, the BioNetGen will produce the MATLAB (The MathWorks, Natick, MA, USA) file needed to simulate the reaction network, which is a model that comprised of 561 non-linear ordinary differential equations (ODEs) predicting the species’ concentrations over time. The MATLAB model file is provided in Supplementary Files S2.

**Model parameters: numerical values and definitions.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Description** | **Unit** | **Model Value** | **Reference and Notes** | |
| **Geometric Parameters** | | | | | |
| Stefanini et al. constructed the first whole body compartmental body of the VEGF system and described the derivations of following geometric parameters in their work2. They later published another modeling work3, which provides a more detailed supplementary table describing the model geometric parameters with experimental measurements. Here we report the value and the sources of parameters used in the model file provided by us. | | | | | |
| BW | Patient Body weight | kg | 70 |  |  |
| Avogadro | Avogadro constant | mol-1 | 6.02e+23 |  |  |
| ECM\_conc | Binding site density of extracellular matrix | M | 7.5e-7 | 4 | \* The binding site density of VEGF and TSP1 are assumed to be the same as FGF. |
| EBM\_conc | Binding site density of the basement membrane surrounding the endothelial cells | 1.3e-5 | 5 |
| PBM\_conc | Binding site density of the basement membrane surrounding the parenchymall cells | 1.3e-5 |
| ECM\_Vol\_tis\_norm | Volume of extracellular matrix of which available to soluble species in normal tissue | cm3/cm3 tissue | 0.061987 | 2,3 | \* The present work models a breast cancer patient of same characteristics as in previous works, which provide the derivation of these geometric parameters and sources of experimental measurements. |
| EBM\_Vol\_tis\_norm | Volume of microvessel basement membrane of which available to soluble species in normal tissue | 8.7e-5 |
| PBM\_Vol\_tis\_norm | Volume of tissue cells basement membrane of which available to soluble species in normal tissue | 3.07e-4 |
| ECM\_Vol\_tis\_blood | Volume of fluid space in blood of which available to soluble species | cm3/cm3 tissue | 0.51931 |
| EBM\_Vol\_tis\_blood | Volume of luminal tumor endothelial cells basement membrane of which available to soluble species | 4.3e-4 |
| PBM\_Vol\_tis\_blood | Volume of luminal healthy endothelial cells basement membrane of which available to soluble species | 0.00421 |
| ECM\_Vol\_tis\_dis | Volume of extracellular matrix of which available to soluble species in breast tumor | cm3/cm3 tissue | 0.51931 |
| EBM\_Vol\_tis\_dis | Volume of microvessel basement membrane of which available to soluble species in breast tumor | 0.00027 |
| PBM\_Vol\_tis\_dis | Volume of tumor cells basement membrane of which available to soluble species in breast tumor | 0.002446 |
| vol\_Norm | Total volume of normal tissue | cm3 | 61321 | 6 |  |
| vol\_Blood | Total volume of blood tissue | 5000 |  |
| vol\_Tumor | Total volume of tumor tissue | 33.51032 |  |
| vol\_Subc | Total volume of subcutaneous compartment | 30 |  |  |
| tumorSA\_Vol\_tis\_dis | Total tumor cells surface area in tumor tissue | cm2/cm3 tissue | 1534 | 7 |  |
| VesselSA\_Vol\_tis\_dis | Total microvessels surface area in tumor tissue | 105 | 8 |  |
| VesselSA\_Vol\_tis\_norm | Total microvessels surface area in normal tissue | 108 | 8 |  |
| fiberSA\_Vol\_tis\_norm | Total tissue cells surface in normal tissue | 664 |  |
| tumorCellSurfArea\_tis\_dis | Surface area of one cancer cell | cm2 | 9.97e-6 | 7 |  |
| VesselCellSurfArea\_blood | Surface are of the luminal side of an endotheali cell (blood) | 1.00e-5 |  |
| VesselCellSurfArea\_tis\_dis | Surface are of the abluminal side of an endotheali cell in tumor tissue | 1.00e-5 |  |
| VesselCellSurfArea\_tis\_norm | Surface are of an abluminal side of an endotheali cell in normal tissue | 1.00e-5 |  |
| fiberCellSurfArea\_tis\_norm | Surface area of skeletal muscle nuclear domain | 1.85e-5 | 8 |  |
| **Secretion Rates** | | | | | |
| The secretion rates of TSP1, MMP3, and proMMP9 are fitted in our study to match the experimental measurements9–12 as mentioned in Method section. The secretion rates of VEGF were fitted to in vivo population PK data in our previous modeling work13. The synthesis rates of a2M were introduced to whole body model in another previous modeling work of us14. | | | | | |
| qTSP1EC | TSP1 secretion rate of endothelial cell in normal tissue (luminal side) | molecules/cell/s | 1 |  | \* The secretion rates of TSP1, MMP3 and proMMP9 for tumor cell and endothelial cells in tumor are based on previous TSP1-VEGF breast tumor tissue model and are further tuned to match the experimental data as mentioned in Methods part.  \*Due to the scarcity of data, we assume the endothelial cells in tumor tissue and in normal tissue have same secretion property. |
| qTSP1disEC | TSP1 secretion rate of endothelial cell in tumor tissue (abluminal side) | 1 |
| qTSP1tum | TSP1 secretion rate of tumor cell | 1 |  |
| qTSP1myo | TSP1 secretion rate of a tissue cell in normal tissue | 0 |  |
| qMMP3\_disEC | MMP3 secretion rate of endothelial cell in tumor tissue | 5 |  |
| qproMMP9\_disEC | proMMP9 secretion rate of endothelial cell in tumor tissue | 1.2 |  |
| qMMP3\_EC | MMP3 secretion rate of endothelial cell in normal tissue | 5 |  |
| qproMMP9\_EC | proMMP9 secretion rate of endothelial cell in normal tissue | 1.2 |  |
| qMMP3\_tum | MMP3 secretion rate of tumor cell | 12 |
| qproMMP9\_tum | proMMP9 secretion rate of tumor cell | 24 |
| qMMP3\_myo | MMP3 secretion rate of a tissue cell in normal tissue | 4 |
| qproMMP9\_myo | proMMP9 secretion rate of a tissue cell in normal tissue | 4 |
| qV165\_tumor | VEGF165 secretion rate of tumor cell | 0.387 | 13 | \* The tumor secretion rates were estimated 15 with experimental measurements 16–19 . The ratio of tumor secreted VEGF165 to VEGF121 is set to be 1:1.  \* The ratio of tumor endothelial cell secreated VEGF165 to VEGF121 is set to 9:1 20. The normal endothelial cell is assumed to have same secretion rate as tumor endothelial cell. The ratio of normal cell secreted VEGF165 to VEGF121 is set to 92:8 21,22. |
| qV121\_tumor | VEGF121 secretion rate of tumor cell | 0.387 |
| qV165\_disEC | VEGF165 secretion rate of endothelial cell in tumor compartment | 0.0324 |
| qV121\_disEC | VEGF121 secretion rate of endothelial cell in tumor compartment | 0.0324\*10/90 |
| qV165\_myo | VEGF165 secretion rate of tissue cell in normal tissue | 5.01e-9 |
| qV121\_myo | VEGF121 secretion rate of tissue cell in normal tissue | 5.01e-9\*8/92 |
| ksyn\_a2M | a2M secretion rate in blood | (mol/cm3 tissue)-1s-1 | 6.27e-14 | 6 |  |
| ksyn\_a2M\_fast | a2M\_ fast secretion rate in blood | 3.14e-14 |  |
| **Recycling of the receptors** | | | | | |
| The recycling rates of receptors are originally from the first tumor tissue model of VEGF-Receptor System by Gabhann et al7. | | | | | |
| sR\_receptors | Recycling rate of unbound receptors | s-1 | 0.00028 | 7 | \*We assume all receptors have same internalization and recycling rates. |
| k\_int\_receptors | Internalization rate of all ligated and unbound receptors | 0.00028 |
| **Kinetic Parameters** | | | | | |
| Gabhann et al applied following kinetic rates of VEGF system in their work of tumor tissue model7 and illustrated the conversion from in vitro parameters to tissue parameters basing on geometric parameters. Following reported values are in vitro parameters, which are converted to tissue parameters used by model during the generation of the MATLAB model file. The kinetic parameters are from our previous tumor tissue model of VEGF and TSP123. | | | | | |
| kon\_TSP1\_GAG | TSP1 binding to glycosaminoglycan | M-1s-1 | 5.00e+5 | 23 | \*The kinetic paramters of TSP1-receptor system are estimated in our previous tumor tissue model of VEGF and TSP1, which included detailed derivations. |
| kon\_TSP1\_CD36 | TSP1 binding to CD36 | 5.00e+5 |
| kon\_TSP1\_CD47 | TSP1 binding to CD47 | 5.00e+5 |
| kon\_TSP1\_LRP1 | TSP1 binding to LRP1 | 2.10e+5 |
| kon\_TSP1\_B1 | TSP1 binding to β1 integrin | 5.00e+5 |
| kon\_TSP1\_VEGF | TSP1 binding to VEGF | 5.00e+5 |
| kon\_TSP1\_MMP3 | TSP1 binding to MMP3 | 1.00e+5 |
| kon\_V165\_N1 | VEGF165 binding to Neuropilin-1 | 3.20e+6 | 24,25 |  |
| kon\_V165\_N2 | VEGF165 binding to Neuropilin-2 | 1.00e+6 | 26–28 | \*~3-50 fold less tight than VEGF165-NRP1 |
| kon\_V165\_R1 | VEGF165 binding to VEGFR1 | 3.00e+7 | 29 |  |
| kon\_V165\_R2 | VEGF165 binding to VEGFR2 | 1.00e+7 | 30,31 |  |
| kon\_V165\_GAG | VEGF165 binding to glycosaminoglycan | 8600 | 32–34 |  |
| kon\_V121\_R1 | VEGF121 binding to VEGFR1 | 3.00e+7 | 13 | \*Set to the same as V165- VEGR receptor |
| kon\_V121\_R2 | VEGF121 binding to VEGFR2 | 1.00e+7 |
| kon\_MMP9\_LRP1 | MMP9 binding to LRP1 | 9245 | 23 |  |
| kon\_MMP3\_proMMP9 | MMP3 binding to proMMP9 | 10000 |  |
| kon\_VEGF\_a2M | VEGF binding to alpha-2-macroglobulin | 25 | 20,35 |  |
| kon\_VEGF\_a2M\_fast | VEGF fast binding to alpha-2-macroglobulin | 250 |  |
| koff\_TSP1\_GAG | TSP1 binding to glycosaminoglycan | s-1 | 0.1 | 23,36,37 |  |
| koff\_TSP1\_CD36 | TSP1 binding to CD36 | 0.115 |  |
| koff\_TSP1\_CD47 | TSP1 binding to CD47 | 0.005 |  |
| koff\_TSP1\_LRP1 | TSP1 binding to LRP1 | 0.0025 |  |
| koff\_TSP1\_B1 | TSP1 binding to β1 integrin | 0.05 |  |
| koff\_TSP1\_VEGF | TSP1 binding to VEGF | 0.005 |  |
| koff\_TSP1\_MMP3 | TSP1 binding to MMP3 | 0.0022303 |  |
| koff\_V165\_N1 | VEGF165 binding to Neuropilin-1 | 0.001 | 24,25 |  |
| koff\_V165\_N2 | VEGF165 binding to Neuropilin-2 | 0.001 | 26–28 |  |
| koff\_V165\_R1 | VEGF165 binding to VEGFR1 | 0.001 | 29 |  |
| koff\_V165\_R2 | VEGF165 binding to VEGFR2 | 0.001 | 30,31 |  |
| koff\_V165\_GAG | VEGF165 binding to glycosaminoglycan | 0.00069 | 32–34 |  |
| koff\_V121\_R1 | VEGF121 binding to VEGFR1 | 0.001 | 13 |  |
| koff\_V121\_R2 | VEGF121 binding to VEGFR2 | 0.001 |  |
| koff\_MMP9\_LRP1 | MMP9 binding to LRP1 | 0.00049 | 23 |  |
| koff\_MMP3\_proMMP9 | MMP3 binding to proMMP9 | 0.001 |  |
| koff\_VEGF\_a2M | VEGF binding to alpha-2-macroglobulin | 1.0e-4 | 20,35 |  |
| koff\_VEGF\_a2M\_fast | VEGF fast binding to alpha-2-macroglobulin | 1.0e-4 |  |
| kc\_V165N\_R2 | Coupling of VEGFR2 and Neuropilin | (mol/cm2)-1s-1 | 1.00e+14 | 38,39 | \*Estimated in 38 using data from 39. |
| kc\_V165R2\_N | Coupling of VEGFR2 and Neuropilin | 3.10e+13 |
| kc\_R1\_N | Coupling of VEGFR1 and Neuropilin | 1.00e+14 | 13 | \*Set to the same as R2-N receptor |
| kc\_CD36\_R2 | Coupling of CD36 and VEGFR2 | 3.10e+11 | 23 |  |
| kc\_CD36\_B1 | Coupling of CD36 and  β1 integrin | 3.10e+13 |  |
| kc\_CD47\_R2 | Coupling of CD47 and VEGFR2 | 3.10e+11 |  |
| kdissoc\_R2\_N | Coupling of VEGFR2 and Neuropilin | s-1 | 0.001 | 38,39 |  |
| kdissoc\_R1\_N | Coupling of VEGFR2 and Neuropilin | 0.01 | 13 | \*Assumed to be slower dissociation than R2-N. |
| kdissoc\_CD36\_B1 | Coupling of VEGFR1 and Neuropilin | 0.001 | 23 |  |
| kdissoc\_CD36\_R2 | Coupling of CD36 and VEGFR2 | 0.001 |  |
| kdissoc\_CD47\_R2 | Coupling of CD36 and  β1 integrin | 0.001 |  |
| **Degradation and Clearance Rates** | | | | | |
| The degradation rates and clearance rates are estimated by conversion from reported half-life time in literatures. The cleavage rate of TSP1 are fitted to match experimental data in our previous work23. The catalytic rate of the activation of proMMP9 by MMP3 and the cleavage of VEGF165 by MMP were previously reported in modeling works by Vempati36,37. | | | | | |
| kdeg\_aV | Degradation rate of bevacizumab | s-1 | 4.415e-8 |  |  |
| kdeg\_VEGF | Degradation rate of VEGF | 1.93e-4 | 40 |  |
| kdeg\_TSP1 | Degradation rate of TSP1 | 3.3e-4 | 23 |  |
| kdeg\_MMP | Degradation rate of MMP | 0.0012 |  |
| kdeg\_TSP1mim | Degradation rate of ABT-510 | 1.60e-4 | 41 | \*Assumed to be same as clearance rate. |
| c\_aV | Clearance rate of bevacizumab in blood | 3.82e-7 | 42 | \*According to FDA label, Bevacizumab has a 21 days half-life. |
| c\_aV\_VEGF | Clearance rate of VEGF-bound bevacizumab in blood | 3.82e-7 | 42 | \*Assumed to be same as free Bevacizumab. |
| c\_VEGF | Clearance rate of bevacizumab in blood | 0.0010797 | 43 |  |
| c\_TSP1 | Clearance rate of TSP1 in blood | 0.00033 | 23 | \* Assumed to be same as degradation rates. |
| c\_MMP | Clearance rate of MMP in blood | 0.0012 |  |
| c\_TSP1mim | Clearance rate of ABT-510 in blood | 1.60e-4 | 41 | \*According to the reported 1.2 hours half-life in circulation of human body. |
| c\_a2M | Clearance rate of alpha-2-macroglobulin in blood | 3.85e-5 | 6 |  |
| c\_a2M\_fast | Clearance rate of alpha-2-macroglobulin fast-binding in blood | 3.85e-3 |  |
| k\_TSP1cleave | The cleavage rate of TSP1 through proteolysis | s-1 | 0.00386 | 23,36,37 |  |
| k\_act\_MMP3\_proMMP9 | A Michaelis-Menten Activation constant of the activation of MMP9 by MMP3 | s-1 | 0.0019 |  |
| kp\_mmp | The proteolysis rate of VEGF by MMPs | (mol/l)-1s-1 | 631 |  |
| **Receptor Numbers** | | | | | |
| The density of VEGF receptors and co-receptors on endothelial and tumor cells are systematically reported in our previous work15, which are taken from in vitro and in vivo measurements using quantitative flow cytometry44. Currently, there is a paucity of quantitative data for the number of TSP1 receptors on endothelial and tumor cells. Thus, we used the reported qualitative data in Human Protein Atlas to estimate the values as mentioned in Method Section. The numbers of receptors on the endothelial cell are set to be half of that for parenchymal cells (tumor cells or muscle fibre cells), assuming equal distribution on the luminal and abluminal surfaces. | | | | | |
| CD36\_number\_tum | CD36 receptor number on tumor cell | receptors/cell | 2500 |  | \*Estimated according the qualitative data shown in Human Protein Atlas. |
| CD47\_number\_tum | CD47 receptor number on tumor cell | 10000 |
| LRP1\_number\_tum | LRP1 receptor number on tumor cell | 5000 |
| B1\_number\_tum | β1 integrin number on tumor cell | 10000 |
| CD36\_number\_disEC | CD36 receptor number on tumor endothelial cell | 1250 |
| CD47\_number\_disEC | CD47 receptor number on tumor endothelial cell | 5000 |
| LRP1\_number\_disEC | LRP1 receptor number on tumor endothelial cell | 2500 |
| B1\_number\_disEC | β1 integrin receptor number on tumor endothelial cell | 5000 |
| CD36\_number\_normEC | CD36 receptor number on normal endothelial cell | 1250 |
| CD47\_number\_normEC | CD47 receptor number on normal endothelial cell | 1250 |
| LRP1\_number\_normEC | LRP1 receptor number on normal endothelial cell | 625 |
| B1\_number\_normEC | β1 integrin receptor number on normal endothelial cell | 2500 |
| CD36\_number\_myo | CD36 receptor number on skeletal muscle fiber cell | 2500 |
| CD47\_number\_myo | CD47 receptor number on skeletal muscle fiber cell | 2500 |
| LRP1\_number\_myo | LRP1 receptor number on skeletal muscle fiber cell | 1250 |
| B1\_number\_myo | β1 integrin receptor number on skeletal muscle fiber cell | 5000 |
| R1\_number\_tum | VEGFR1 receptor number on tumor cell | 1100 | 15 | \*VEGF receptor density followed our previous studies which uses the in vivo and in vitro measurements using quantitative flow cytometry. |
| R2\_number\_tum | VEGFR2 receptor number on tumor cell | 550 |
| N1\_number\_tum | Neuropilin-1 receptor number on tumor cell | 39500 |
| N2\_number\_tum | Neuropilin-2 receptor number on tumor cell | 39500 |
| R1\_number\_disEC | VEGFR1 receptor number on tumor endothelial cell | 3750 |
| R2\_number\_disEC | VEGFR2 receptor number on tumor endothelial cell | 300 |
| N1\_number\_disEC | Neuropilin-1 receptor number on tumor endothelial cell | 20000 |
| N2\_number\_disEC | Neuropilin-2 receptor number on tumor endothelial cell | 20000 |
| R1\_number\_normEC | VEGFR1 receptor number on normal endothelial cell | 550 |
| R2\_number\_normEC | VEGFR2 receptor number on normal endothelial cell | 350 |
| N1\_number\_normEC | Neuropilin-1 receptor number on tumor endothelial cell | 17000 |
| N2\_number\_normEC | Neuropilin-2 receptor number on tumor endothelial cell | 0 |
| R1\_number\_myo | VEGFR1 receptor number on skeletal muscle fiber cell | 0 |
| R2\_number\_myo | VEGFR2 receptor number on skeletal muscle fiber cell | 0 |
| N1\_number\_myo | Neuropilin-1 receptor number on skeletal muscle fiber cell | 34500 |
| N2\_number\_myo | Neuropilin-2 receptor number on skeletal muscle fiber cell | 0 |
| **Transportation Rates** | | | | | |
| The vascular permeability of VEGF uses the rates estimated in the first whole body model of VEGF basing on the size of molecule2. The lymphatic flow was introduced into the model in another work later43. | | | | | |
| k\_lymph\_dis | The transport rate through lymphatic flow from tumor to blood | cm3/s | 0 | 43 | \*Assumed to be negligible. |
| k\_lymph | The transport rate through lymphatic flow from normal tissue to blood | 0.0333333 |  |
| kperm\_B\_T\_VEGF | Microvascular permeability to VEGF in the tumor | cm/s | 4.0e-7 | 2 |  |
| kperm\_B\_N\_VEGF | Microvascular permeability to VEGF in the normal tissue | 4.0e-8 |  |
| kperm\_B\_T\_aV | Microvascular permeability to Bevacizumab in the tumor | 3.0e-7 | \*Assumed to be smaller than VEGF |
| kperm\_B\_N\_aV | Microvascular permeability to Bevacizumab in the tumor | 3.0e-8 |
| **Properties of the Anti-angiogenic Drugs** | | | | | |
| The binding properties of VEGF are directly measured in an experimental study45. | | | | | |
| antiVEGF\_dosage | Administration dosage of Bevacizumab | mg/kg | 10 |  |  |
| antiVEGF\_MW | Molecular weight of Bevacizumab | Da | 150000 |  |  |
| infTime\_antiVEGF | Infusion time of Bevacizumab | s | 5400 |  | \* infusion in 1.5 hours. |
| Kd\_V165\_antiVEGF | The dissociation constant of Bevacizumab and VEGF165 | M | 2.2e-9 | 45 |  |
| Kd\_V121\_antiVEGF | The dissociation constant of Bevacizumab and VEGF121 | 2.2e-9 |  |
| koff\_V165\_antiVEGF | The binding of Bevacizumab and VEGF165 (koff) | s-1 | 2.0e-4 |  |
| koff\_V121\_antiVEGF | The binding of Bevacizumab and VEGF165 (koff) | 2.0e-4 |  |

\* Here, M = moles/liter of interstitial fluid available to soluble species.

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